

BLA Clinical Review Memorandum

Application Type	Original Application
STN	125612/0
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Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	Victor C. Baum, M.D; Bindu George, M.D.
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Supervisory Concurrence	Tejashri Purohit-Sheth
Applicant	Octapharma Pharmazeutika Produktionsges.m.b.H.
Established Name	Fibrinogen (human)
(Proposed) Trade Name	Fibryna®
Pharmacologic Class	Freeze-dried human fibrinogen
Formulation(s), including Adjuvants, etc.	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized powder in single-use bottles containing 1g fibrinogen to be reconstituted with 50 mL water for injection
Dosing Regimen	Based on target plasma fibrinogen level: Dose (mg/kg) = [target level (mg/dL) - measured level (mg/dL)] / 1.8 (mg/dL / mg/kg) If baseline level unknown: 70mg/kg
Indication(s) and Intended Population(s)	Acute bleeding episodes and adult and adolescent patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
Orphan Designated (Yes/No)	No

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GLOSSARY

AA	accelerated approval
AC	advisory committee
AE	adverse event(s)
AUC _{norm}	area under the curve, normalized for actual dose
BE	bleeding episode(s)
C _{max}	maximum plasma concentration
CFD	congenital fibrinogen deficiency
CI	confidence interval
CL	clearance
DVT	deep venous thrombosis
EMA	European Medicines Agency
FAS	full analysis set
FC	fibrinogen concentrate
FFP	fresh frozen plasma
FRT	fibrinogen replacement therapy
GLP	good laboratory practices
IDMEAC	independent data monitoring and endpoint adjudication committee
ICH	intracranial hemorrhage
ITT	intention to treat
I.V.	intravenous
IVR	in vivo recovery
MCF	maximum clot firmness
PD	pharmacodynamics
PeRC	pediatric review committee
PI	prescribing information
PK	pharmacokinetics
PK-PP	pharmacokinetics analysis set
PMR	post marketing requirement
PP	per protocol
ROTEM	rotational thromboelastometry
TEAE	treatment emergent adverse event
(b) (4)	
WFI	water for injection

1. Executive Summary

STN 125612 is an original biologics license application (BLA) submitted by the applicant, Octapharma Pharmazeutika Produktionsges for plasma-derived fibrinogen from pooled U.S. (b) (4) plasma under the proposed proprietary name Fibryna (previously used name Octafibrin). The clinical studies were undertaken under IND 14777. The proposed indications are for the treatment of acute bleeding episodes (BE) (b) (4) in adults and children with congenital fibrinogen deficiency (Fibryna is not indicated for dysfibrinogenemia).

Two studies formed the basis for the safety and efficacy of Fibryna for the proposed indications: FORMA 01 and FORMA 02. The safety, pharmacokinetic (PK) and pharmacodynamic (PD) data from one completed clinical study (FORMA 01) were provided as supportive of the data from FORMA 02 study. FORMA 02 is an ongoing study in adult and adolescent subjects for the treatment of acute bleeding and perioperative prophylaxis. The data in this submission relates to the interim analyses results for the treatment of bleeding events and surgical prophylaxis in 13 subjects.

FORMA 01 was a phase 2 crossover pharmacokinetic (PK) and PD study in 22 subjects ≥ 12 years old (range 12 to 53 years, 16 adults and 6 adolescents, primary analysis in 21 subjects) with congenital fibrinogen deficiency comparing the PK and PD of Fibryna to the U.S. licensed comparator fibrinogen concentrate product RiaSTAP¹. A single dose of Fibryna at 70mg/kg was administered i.v. The assessment of efficacy results based on PK and PD parameters is deferred to the Clinical Pharmacology review discipline. However the clinical reviewer concluded that the mean plasma fibrinogen levels of 125 mg/dL achieved one hour post infusion in 19 subjects is supportive of the efficacy findings from the FORMA 02 study. There were no deaths, no thrombotic events, hypersensitivity reactions or immune related adverse events noted in this study. There were no serious adverse events that were related to Fibryna.

FORMA 02 is an ongoing uncontrolled Phase 3 safety and efficacy study of Fibryna used for on-demand treatment of bleeding episodes and for perioperative prophylaxis in patients ≥ 12 years old (range 13-53 years. This study is ongoing (projected conclusion Quarter 4, 2020). Subjects were to be dosed to target plasma levels of fibrinogen using the (b) (4) assay of 100 mg/dL for treatment of minor bleeding and minor surgery and 150 mg/dL for treatment of major bleeding or pre-operatively and intra-operatively during surgery. Data from 11 adults and two adolescents are available for review through the planned interim analysis. Efficacy outcomes based on separate four point scales for treatment of bleeding events and perioperative bleeding were determined by the investigator and independent data monitoring and endpoint adjudication committee (IDMEAC). For the purpose of primary efficacy analyses, hemostatic efficacy was considered successful if excellent to good hemostasis was achieved at 24 hours following administration of Fibryna in cases of acute bleeding, following completion of surgery for perioperative management and confirmed by the IDMEAC. The primary efficacy was to

¹ In this BLA the applicant uses the term Haemocompletan® P/RiaSTAP™ RiaSTAP is the name of the licensed product in the U.S.

be assessed based on the outcomes of the first bleeding event or during the perioperative period for any surgery. The pre-specified endpoint for study success was based on achieving a lower bounds of the two sided 90% Blyth-Still-Castella CI of > 0.70 .

Eleven subjects experienced their first bleeding event on study. However, per FDA analysis, 10 subjects were evaluable for the first bleeding events. One subject who achieved successful hemostasis was excluded because the subject received a sub-therapeutic dose that resulted in no change from baseline to post infusion plasma fibrinogen levels. The baseline level of this subject was determined to be diagnostic of afibrinogenemia. The hemostatic efficacy for the primary efficacy evaluable population of 10 subjects was 100% with the lower bounds of 90% CI at 0.78. The study thus met the protocol defined success criterion. Of the 23 bleeding events submitted to the BLA, 22 were considered evaluable for hemostatic efficacy. Twenty one of the 22 bleeding episodes had successful hemostatic outcomes. The hemostatic efficacy was 95% with the 90% lower bounds of the CI at 0.80. For one bleeding episode, the efficacy assessment was missing and therefore considered a treatment failure by the FDA reviewer. The result of the secondary efficacy analysis for hemostatic efficacy for all bleeding episodes is supportive of the primary efficacy findings. None of the 23 bleeding events were major bleeding events.

Four of the eleven subjects enrolled into the study underwent four surgical procedures and received Fibrina for perioperative management of bleeding. Of the four surgical procedures, one was considered to be major surgery (enucleation of the eye) by the Applicant with an estimated maximal blood loss of 100ml. The remainder of the surgeries was minor and included a single tooth extraction, circumcision and synovectomy of the knee. The outcomes were considered to be successful. (b) (4)



Although, there is limited efficacy and safety data for doses required to treat major bleeding, there is sufficient data from the clinical studies to support approval of FIBRYNA for the treatment of major and minor bleeding in this rare disorder. The efficacy data are adequate to demonstrate efficacy based on the primary and secondary analysis of acute minor bleeding events in the FORMA-02 study in subjects dosed to target a level of 100 mg/dL. The safety of the dose targeted to achieve plasma fibrinogen level of 100mg/dL is adequately characterized based on the safety data in 16 bleeding episodes and three surgical procedures where the plasma fibrinogen levels post-infusion ranged from 79-139 mg/dL and is further supported by data from the published literature. The data to support the efficacy of FIBRYNA for an indication in major bleeding is based on documentation of successful hemostasis in a) subjects who achieved target

fibrinogen levels of > 140 mg/dL following treatment of six BEs and b) the single subject who underwent major surgery who achieved target plasma fibrinogen levels of 220 mg/dL. Additionally, the published data supports control of bleeding at lower plasma fibrinogen levels of 100mg/dL. The safety profile based on the results of the pooled analysis of FORMA- 01 and FORMA-02 of Fibryna and specifically in the seven subjects who achieved target plasma fibrinogen levels >140 mg/dL facilitates assessment of safety to a limited extent in subjects who were dosed to target plasma fibrinogen level of 150 mg/dL. None of these seven subjects experienced thrombotic events, deaths or discontinuations resulting from an adverse event. Therefore, the overall risk-benefit assessment favors marketing approval of Fibryna in major and minor indication with the caveat that the anticipated risks of thrombosis have yet to be adequately quantified for the dose targeted to achieve plasma fibrinogen level of 150 mg/dl (the recommended dose for treatment of major bleeding). The paucity of safety data for treatments that target fibrinogen levels of 150 mg/dL in the FORMA 02 study and the published literature limit a robust assessment of the thrombotic risks. In addition, based on the published literature, the risks of thrombosis following fibrinogen replacement therapy (FRT) either as cryoprecipitate and fibrinogen concentrates exists at lower target plasma fibrinogen level (100 mg/dL). Therefore these risks may be higher with higher target plasma fibrinogen levels. The anticipated thrombotic risks with Fibryna (a fibrinogen concentrate) dosed to 150 mg/dL, form the basis for the recommendation for a post marketing required study to analyze the thrombotic risks at this dose.

An additional trial, FORMA-04 is an ongoing trial (IND 14777.20) assessing efficacy and safety of Fibryna in children ≤ 12 years of age with congenital fibrinogen deficiency. The expected completion date for this study is 31st October 2021. 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. No data from that trial were provided in the BLA submission.

The recommendations for post-marketing actions include:

- Post marketing study to evaluate the risks of thromboembolic events, hypersensitivity reactions in adults and adolescent subjects.
- Submission of the results of the ongoing FORMA-04 to satisfy the PREA requirements for the approved indication in adults and adolescents for the treatment of acute bleeding events.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

FORMA 01:

- 14 (64%) White, 8 (36%) Asian
- 6 were 12 to <18 years of age; 4 were 12 to 16 years of age
- 15 females (68%) and 7 males (32%)

The sample size was small. However, there were no notable differences in the post-treatment plasma fibrinogen levels achieved either based on sex or by age..

FORMA 02:

- 9 (69%) White, 3 (23%) Asian, 1 (8%) Other (Arab)
- 1 was Hispanic/Latino
- 2 were 12 to <18 years of age
- 6 (46%) females and 7 (54%) males

There was no difference in clinical hemostatic efficacy when the data were analyzed by sex or race, and there were no apparent differences by age.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Fibrinogen or Factor 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 Factor XIII to form a clot. The three genes coding for fibrinogen B β (*FGB*), A α (*FGA*) and γ (*FGG*), on chromosome 4 are responsible for the production of A α , B β and γ -polypeptide which polymerize to form insoluble fibrin. Normal fibrinogen level measured by the Clauss method, range from 150-350 mg/dL and fibrinogen has a half-life of 3-5 days. The critical plasma fibrinogen level below which hemorrhage usually occurs in patients is approximately 0.5 – 1.0 g/L. In case of major surgical intervention, precise monitoring of replacement therapy by coagulation assays is essential.

Congenital fibrinogen deficiency 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 concentration to ≤ 150 mg/dL), dysfibrinogenemia (dysfunctional fibrinogen) and hypodysfibrinogenemia (both reduced quantity and quality). The estimated prevalence of afibrinogenemia is approximately 1:1,000,000,² although the prevalence increases in areas of increased consanguinity, and registries in the United Kingdom and Italy show a lower prevalence, approximately 1:6,000,000.³

The clinical manifestation of afibrinogenemia presents with highly variable bleeding phenotypes. Bleeding occurs in 78% of patients with afibrinogenemia, with 10% of the bleeding events being intra-cranial bleeding which is a major cause of death in patients with afibrinogenemia. Neonatal bleeding such as bleeding from the cord stump is usually 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 events (BE)

² Peyvandi F, Bolton-Maggs PH, Batorova A and De Moerloose P. Rare bleeding disorders. *Haemophilia* 2012; 18 Suppl 4: 148-53.

³ Lak M, Keihani M, Elahi F, Peyvandi F and Mannucci PM. Bleeding and thrombosis in 55 patients with inherited afibrinogenemia. *Br J Haematol* 1999; 107: 204-6.

varies from none to multiple episodes per year. The reported frequency of is 0.7 bleeding episodes per year.⁴ The symptoms of hypofibrinogenemia are usually milder. These subjects can be asymptomatic, but are at risk for excessive bleeding with trauma. Fibrinogen will not be indicated for the treatment of dysfibrinogenemia. Dysfibrinogenemia has the risk of bleeding as well as thrombotic risk, however the severity of the bleeding and thrombotic risks are lower than with patients with congenital afibrinogenemia and hypofibrinogenemia.

Of the rare congenital hematological bleeding disorders, congenital afibrinogenemia is associated with the highest risk of thrombosis. These thrombotic events are arterial or venous in nature and occur even in the absence of fibrinogen replacement therapy (FRT).⁵ In a retrospective study of 55 patients with afibrinogenemia, the spontaneous rate of thrombosis was noted to be 4% with one case of arterial thrombosis and 1 case of sagittal sinus thrombosis.⁶

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

Although FC products were approved in the U.S. for treatment of CFD, the marketing licenses were revoked in 1977 for risks of hepatitis infection and suspected lack of efficacy.⁷ Haemocomplettan® manufactured by CSLB has been approved in some countries since 1985 after improvements in safety and purity. In the United States (U.S.) a human fibrinogen concentrate (RiaSTAP®) manufactured by CSLB from pooled plasma was approved by the FDA in 2009 for treatment of acute bleeding episodes in patients with afibrinogenemia and congenital hypofibrinogenemia. In the U.S., besides fibrinogen concentrate (FC), other available sources of fibrinogen for FRT but not approved by the FDA, may be used and these include cryoprecipitate and fresh frozen plasma (FFP). In the U.S. FC remains the most favored form of FRT.

4 Peyvandi F, Haertel S, Knaub S and Mannucci PM. Incidence of bleeding symptoms in 100 patients with inherited afibrinogenemia or hypofibrinogenemia. *J Thromb Haemost* 2006; 4: 1634-7.

5 [Girolami A](#)¹, [Ruzzon E](#), [Tezza F](#), [Scandellari R](#), [Vettore S](#), [Girolami B](#). Arterial and venous thrombosis in rare congenital bleeding disorders: a critical review. [Haemophilia](#). 2006 Jul;12(4):345-51

6 Lak M, Keihani M, Elahi F, Peyvandi F, Mannucci PM. Bleeding and thrombosis in 55 patients with inherited afibrinogenemia. *Br J Haematol* 1999; 107: 204-6.

7 Final Clinical Review Memo (redacted) 125317/0

<https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm089277.htm>

FRT and dosing of fibrinogen is primarily based on the Guidelines issued in 2004 by the United Kingdom Haemophilia Center Doctors' Organization.⁸ 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 3) secondary prophylaxis following a life-threatening bleeding to minimize the risk of re-bleeding with trough levels aimed at 50mg/dL.

RiaSTAP an FC is approved in the U.S under the Accelerated Approval Path in 2009. While both RiaSTAP and Fibryna are FC products, the most notable difference in manufacturing between the two products relates to viral inactivation. Fibryna requires two viral inactivation steps whereas RiaSTAP requires (b) (4) inactivation step. The approval of RiaSTAP was based on the surrogate endpoint of Maximum Clot Firmness (MCF) demonstrated by rotational thromboelastography method (ROTEM) following administration of a single dose of the product in the non-bleeding state in subjects with CFD.

The most notable risks from FRT in patients with CFD especially those with congenital afibrinogenemia relate to thrombosis, hypersensitivity reactions and transmissible infectious agents. Given the paucity of safety data with approved products for FRT and in this BLA submission, the published literature was reviewed to quantify the thrombotic and hypersensitivity risks associated with FRT. A retrospective case report evaluated 50 subjects with CFD, who received FRT with FC, cryoprecipitate or FFP. The dose of FRT was to target a level of 100 mg/dL for either treatment of acute bleeding, prophylaxis or perioperative management. Of the 50 subjects, twenty two subjects were treated for life-threatening bleeding either during the acute bleeding event or as follow-on prophylaxis to reduce the risk of near future bleeding.⁹ Five of the 22 patients experienced thrombotic events. Three of five thrombotic events occurred during prophylaxis of which two of the three were related to FC and one of three were related to cryoprecipitate. Of the remaining two subjects who received FRT for reasons other than prophylaxis and experienced thrombosis, one subject received high dose FC and the other subject received concomitant FVII product (which is associated with risks of thrombosis). Of the 22 subjects, two subjects on FC developed anaphylactic reaction with development of inhibitory antibodies to fibrinogen. In a prospective study of 9 subjects with CFD who received FRT, 5 subjects had congenital afibrinogenemia.¹⁰ Seven of the 9 subjects experience a thromboembolic event and had atrial fibrillation as an underlying risk factor.

8 Bolton-Maggs, P, Perry D, Chalmers E, Parapia L, Wilde, Williams M, Collins P, Kitchen S, Dolan G, Mumford, A. The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. *J.Haemophilia* (2004), 10,593-628

9 *Journal of Thrombosis and Haemostasis*, 9: 1687–1704 Bornikova L, Peyvandi F, Allen G, Bernstein J, Manco-Johnson MJ. Fibrinogen replacement therapy for congenital fibrinogen deficiency. *J Thromb Haemost* 2011; 9: 1687–704.

10 Rottenstreich A, Lask A, Schliamser L, Zivelin A, Seligsohn U, Kalish Y. Thromboembolic events in patients with severe inherited fibrinogen deficiency. *J Thromb Thrombolysis* (2016) 42:261–266

Five of the seven subjects experienced venous thromboembolic events while on FRT, while two subjects experienced arterial thrombosis and were not on FRT.

Reviewer comments

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, however, there are limitations with the available data in that prospective studies are single arm and of limited size and data from case report reviews are subject to selection bias and therefore should be interpreted with caution. The overall conclusions of the studies referenced above are that FRT should be used with caution and thrombotic events occur with concomitant use of FRT. Given the rare nature of the disease and the availability of FRT, in this reviewer's opinion it is unfeasible and unethical to conduct studies to collect data to understand the natural history of the disease to better assess the underlying risks of spontaneous thrombosis. The prevalence of CFD in areas of consanguinity and absence of genetic heterogeneity and variable nature of the severity of bleeding further limit the robustness of the data obtained from published literature. The Guideline for treatment as proposed by the UK guideline although widely utilized is not supported by a robust evidence based data. Note should be made that the Guideline recommends target plasma fibrinogen levels of 100 mg/dL for the management of major bleeding and perioperative management and maintenance of trough levels of 50 mg/dL until wound closure. Therefore, the target plasma fibrinogen level for the treatment of bleeding and perioperative prophylaxis based on the recommendations in the Guideline, is lower than the target levels of 150 mg/dL as proposed in the FORMA 02 study for treatment of major bleeding and perioperative management for hemostatic control. Although it is unclear whether a dose-dependent effect on thrombotic risks exists, higher target levels could result in longer exposures to FRT and may have the potential to increase the thrombotic risks.

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

Current therapy consists of replacement therapy for bleeding episodes (BE). Available FRT include fresh frozen plasma (FFP), cryoprecipitate, fibrinogen concentrate, and the licensed fibrinogen (from pooled human plasma) RiaSTAP (CSL Behring), all targeted to achieve a plasma concentration of fibrinogen of 100 mg/dL. Please see Section 2.1 for further details.

RiaSTAP received marketing exclusivity which expired on January 16, 2016.

2.3 Safety and Efficacy of Pharmacologically Related Products

Given in adequate doses, both FFP and cryoprecipitate are effective. Given the low fibrinogen concentration compared to fibrinogen concentrates, FFP and to some extent cryoprecipitate require larger volume infusions. They also do not have viral inactivation steps and contain additional plasma proteins such as fibronectin, von Willebrand factor, and possible allergens. FFP also carries a risk of transfusion-related acute lung injury

(TRALI). The amount of fibrinogen in these products is variable and unknown, and transfusion of multiple units is required. These products also require thawing before use. Although there are several commercially prepared fibrinogen concentrates, only a single one, RiaSTAP is approved for use in the U.S.

For the purposes of RiaSTAP approval, MCF was considered a pharmacodynamic (PD) measure of fibrinogen content and effects of FRT in clinical practice based on review of the published literature. This was further supported by the demonstration of changes to MCF using thromboelastography (TEG) following fibrinogen supplementation of fibrinogen-deficient plasma. Subjects with congenital afibrinogenemia in the non-bleeding state were administered a single dose of 70mg/kg and the mean change in MCF pre and 1hour post-infusion without a pre-specified study success criteria for hypothesis testing. The results of the study demonstrated that the mean change in MCF values closely approximated levels expected from adding known amounts of fibrinogen to plasma in-vitro. Pharmacokinetic studies were evaluated in children and adults and provided data in support of efficacy. A post-marketing required study to confirm the clinical efficacy and correlation between the mean change in MCF and hemostatic efficacy is underway. (b) (4)

. The dose for RiaSTAP is individualized and based on desired target levels and known pre-treatment plasma fibrinogen levels. The prescribing information (PI) for RiaSTAP recommends targeting a level of 100mg/dL of fibrinogen until hemostasis is achieved. No adverse events were noted following the single administration at the flat dose in the study evaluating MCF to support approval through AA. In other clinical studies and post-marketing surveillance, treatment with RiaSTAP has been associated with allergic and anaphylactic reactions, thromboembolic episodes, myocardial infarction, pulmonary embolism, deep vein and arterial thrombosis.

In general, FRT with cryoprecipitate, FFP and FC products approved in other countries have been associated with risks of thrombosis and hypersensitivity reactions based on the review of published literature.

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

Fibryna is not currently licensed for clinical use in any jurisdiction. The studies reported in this BLA represent the entire human experience, with the exception of ongoing trials.

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

Correspondence History:

- Pre-IND meeting on November 30, 2010 (CRMTS #7718).
 - o FDA agreed to a clinical development plan based on a surrogate endpoint (maximum clot firmness) proposed in support of approval through the accelerated approval path. FDA advise the Applicant that it was unlikely that Fibryna would demonstrate therapeutic benefit to patients over existing treatment (RiaSTAP) therefore it was unlikely that an accelerated approval would be applicable. The post-approval study to demonstrate

hemostatic efficacy would be based on demonstrating non-inferiority with RiaSTAP.

- IND Submission: July 22, 2011 with a proposal for the Phase 2 study (FORMA 01) evaluating MCF as a surrogate endpoint for hemostatic efficacy.
- IND advice teleconference minutes, August 24, 2011
 - FDA noted that the accelerated approval path was not applicable for Fibryna, as an unmet need did not exist subsequent to the approval of RiaSTAP.
 - As maximum clot firmness had not yet been validated, FDA wanted to view efficacy data on ≥ 10 subjects at the time of licensure. Octapharma noted this was similar to the approach taken by (b) (4) regulators. FDA requested that Applicant submit the Phase 3 study for review.
- IND advice telecommunication (via email), September 14, 2011. With regard to the FORMA 01 study, the FDA requested that :
 - The Applicant contact the Office of Orphan Drugs as exclusivity for the proposed indication was held by RiaSTAP
 - Include monitoring criteria for early signs of hypersensitivity reactions
 - Exclude dysfibrinogenemia
- IND submission of the FORMA 02 study on December 14, 2011. No FDA communications to the Applicant regarding this submission was noted in the electronic document room.
- IND submission of a revised protocol for FORMA 02 study under Amendment 3 on January 30, 2013, relate to:
 - Revisions to the surgical protocol
 - Exclusion of subjects with dysfibrinogenemia and pregnant women within 20 weeks of gestation
 - Inclusion of subjects 12-17 years of age
 - Proposal for a formal hypothesis testing based on successful hemostatic efficacy of $>70\%$
- On November 23, 2013, FDA reviewed the revised Phase 3 FORMA 02 study submitted under Amendment 8 of IND 14777 and provided the following comments to the following revisions:
 - The primary efficacy endpoint was to be based on assessment of hemostatic efficacy for the first bleeding episode. Assessment of hemostatic efficacy for the subsequent bleeding episodes was a secondary endpoint. FDA requested justification for evaluating only the first bleeding episode for the primary efficacy analysis.

- o The FDA requested that the Independent Endpoint Adjudication Committee (IDEAC) rather than Independent Data Monitoring Committee (IDMC) adjudicate final efficacy assessment for each subject.
 - o An objective measure for restoration of hemostasis was requested.
- Advice/information request letter, April 14, 2016
 - o Addressed the issue of including all versus only the first BE for any patient as the primary endpoint in study FORMA 02, rather than all BE. The applicant indicated that this had been addressed by the (b) (4) [REDACTED]. Cumulative BE will be analyzed as a secondary analysis.
 - o Octapharma asked to enroll 6 subjects in the BE and perioperative groups in FORMA 02 (or continue until 5 years, whichever comes first).
 - o FDA queried the minimum number of BE that would be included. Extrapolation of efficacy to pediatric patients may be dependent on having sufficient PK data as well as adequate efficacy data in adults.
 - o FDA advised Octapharma to ensure formal assessment of thromboembolic effects.
 - o The FORMA 02 and FORMA-04 protocols had also been approved by the pediatric committee of the (b) (4) [REDACTED] and the study had started enrollment and will complete the criteria for the conduct of the interim analysis shortly. This interim analysis was agreed with the agency to be the pivotal data needed, along with the final comparative PK study (FORMA 01), for submission of the BLA for this indication.
 - o The final efficacy assessment by the Independent Data Monitoring and Endpoint Adjudication Committee (IDMEAC) will be the assessment used for the primary efficacy analysis.
- Pre-BLA meeting (CRMTS#10194), April 22, 2016
 - o Octapharma inquired if the proposed clinical package would suffice for the indication “Treatment of acute bleeding episodes (b) (4) [REDACTED] in adult and pediatric patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia”. FDA responded determination for licensure will be made upon review of the data provided with the BLA.
 - o In an advice letter sent under IND 14777 on April 15, 2016, FDA requested that the Applicant include in the BLA submission additional analyses, analyzing data by sex (appreciating the small number of subjects) and assessment of AEs by the applicant in addition to the assessment of AEs by the investigators.

Reviewer’s Note: To fulfill this request, addenda to the clinical study reports have been prepared and are included in this BLA submission.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. It was provided electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The studies supporting this submission were conducted in compliance with good clinical practices, including informed consent, site-specific issues, and in accordance with acceptable ethical standards. The following international sites were inspected by FDA Bioresearch Monitoring (BIMO).

FORMA 01 - Study site #11, Bangalore, India & Study Site #51, London, U.K.

FORMA 02 - Study site # 91, Bangalore, India & Study Site #10, London, U.K.

Applicant-identified protocol deviations

No subject was discontinued from either study due to a protocol violation. Two subjects in FORMA 02 were excluded from per-protocol populations. One subject received 81% of the planned dose and one subject received 54% of the planned dose.

Reviewer's comment: Subject (b) (6) was under dosed and had fibrinogen levels that were unchanged from baseline at one and three hours following the infusion. This was considered a major protocol deviation. Subject (b) (6) was under dosed but achieved the protocol specified target fibrinogen level. This event was considered a minor protocol deviation.

3.3 Financial Disclosures

Covered clinical study (name and/or number):FORMA 01		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>10</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered clinical study (name and/or number): FORMA 02		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>14</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

No significant concerns were raised following review of financial disclosures.

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

4.1 Chemistry, Manufacturing, and Controls (CMC)

Fibryna is manufactured from plasma collected in the U.S. For details of the manufacturing process, please refer to the CMC review.

Table 1: Impurities and excipients per mL final solution

(b) (4)	(b) (4)
(b) (4)	(b) (4)
Glycine	(b) (4)
L-Arginine HCl	(b) (4)
Citrate	(b) (4)
Chloride	(b) (4)

Source: BLA 125612, Nonclinical Overview, page 5 of 40.

Reviewer's comment

The first two are process-related impurities and the last four are excipients. (b) (4) [REDACTED], are process related impurities. The levels of (b) (4) [REDACTED] in the final product (50 mL) are similar to those for (b) (4) [REDACTED], an approved product. The risk of these levels of impurities was also addressed in the non-clinical studies for (b) (4) [REDACTED]. The level of glycine in the final product is less than for Octaplas. The levels of the other three excipients (citrate, chloride and L-arginine HCl are similar to those for RiaSTAP. The toxicology information regarding final levels of the product is being deferred to the CMC and Pharmacology Toxicology review divisions.

4.2 Assay Validation

In the FORMA 02 study, the (b) (4) [REDACTED] assay performed in a central laboratory was used to measure baseline and post-infusion plasma fibrinogen activity levels.

Reviewer's comment: The (b) (4) assay is used in clinical practice for assessment of plasma fibrinogen activity level. This assay was used to determine fibrogen activity in the pharmacokinetic studies to evaluate efficacy of (b) (4) as stated in the prescribing information. The analytical validation of the (b) (4) assay was performed as part of the potency assay for the manufacturing of the product. For these reasons additional validation studies for the clinical study were not considered necessary.

4.3 Nonclinical Pharmacology/Toxicology

For details of the discussion and results of the studies related to pre-clinical studies, please refer to the Pharmacology-Toxicology review memo.

Reviewer's comment: No significant safety concerns/signals were identified per the pharmacology/toxicology review. For additional details please refer to review memo by the pharmacology toxicology discipline.

4.4 Clinical Pharmacology

Evaluation of clinical pharmacology of Fibryna was an important component of both clinical studies.

4.4.1 Mechanism of Action

Fibryna is obtained from pooled human plasma and directly restores functional fibrinogen levels in patients with congenital afibrinogenemia or hypofibrinogenemia, allowing cleavage by thrombin and subsequent clot formation.

4.4.2 Human Pharmacodynamics (PD)

The pharmacodynamic effects of Fibryna are the same as those of endogenous fibrinogen.

4.4.3 Human Pharmacokinetics (PK)

See efficacy analysis for Trial 1 ([section 6.1.11](#)). In brief, the PK results for Fibryna were similar to those of the licensed comparator product.

4.5 Statistical

Statistical analyses were based on the methods outlined in version 1.0 of the Statistical Analysis Plan (January 13, 2015). Missing data were not imputed. Additional analyses were requested by FDA. In the pre-BLA meeting of April 15, 2016, FDA requested that efficacy data be shown using a two-sided 95% CI rather than the original 90% CI proposed by Octapharma. These analyses are included in addenda to the study reports. The primary efficacy analysis is based on the two sided 90% CI as proposed by the Applicant and reviewed by the FDA in November 2013.

4.6 Pharmacovigilance

As part of the routine pharmacovigilance surveillance, MedDRA queries will be used to

review cases from the Drug Safety Database to identify potential risks as well as missing information. Additionally, two further trials will investigate the efficacy and safety of Fibryna in the age group ≥ 12 years (the continuing trial FORMA 02) and in pediatric patients (< 12 years) (trial FORMA-04, which has begun recruitment).

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

5.1 Review Strategy

Final data from Studies FORMA 01 and FORMA 02 were reviewed, as were prior communications with the applicant and review of the relevant IND (IND 14777) related documents. Since the FORMA-02 study relates to hemostatic efficacy in bleeding subjects and the perioperative management of subjects with CFD, the clinical review strategy is focused on review of this study for the assessment of efficacy for hemostasis and perioperative management in adults and adolescent subjects. The safety data from the FORMA-01 and -02 study were evaluated to determine safety. In the FORMA-02 study, the hemostatic efficacy results did not include data from pediatric subjects < 12 years of age. A separate study, FORMA-04, is planned.

The Applicant proposes in the future, to seek an indication for all pediatric age groups. Therefore, the conclusions by the Clinical Pharmacology review discipline with regard to PK and PD assessments in different age groups in the FORMA-01 study and the hemostatic efficacy data from the FORMA-02 study in the adolescent age group was used to determine the extent of extrapolation that would be feasible from the adult and adolescent subjects to support an indication in children ≤ 12 years of age.

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

- 1.2 Cover Letter
 - 1.3.3 Debarment Certification
 - 1.3.4 Financial Disclosure
 - 1.9 Pediatric Administrative Information
 - 1.12 Other Correspondence
 - 1.18 Proprietary Names
 - 2 Common Technical Document Summaries
 - 4 Nonclinical Study Reports
 - 5 Clinical Study Reports
- IND14777

5.3 Table of Studies/Clinical Trials

Protocol	Type	Phase	Design	# Subjects	Primary Endpoint(s)	Status
FORMA 01	PK, efficacy, safety	2	Multinational, prospective, randomized, crossover	16 adults 6 adolescents	1) AUC _{norm} of Fibryna versus comparator 2) Maximum clot firmness versus	Completed

					comparator	
FORMA 02	“Pivotal”, efficacy, safety	3	Multinational. prospective, open-label, uncontrolled,	11 adults, 2 adolescents	Hemostatic efficacy in on-demand treatment of BE	Ongoing

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee (AC) meeting was waived by Office of Tissue and Advanced Therapies (OTAT) for the following reasons:

- o The drug is not the first in class. An AC meeting regarding accelerated approval of RiaSTAP was held on January 9, 2009.
- o In addition, no controversial issues were identified in this application that would benefit from an AC discussion.
- o Serious adverse events were not noted both in FORMA-01 and FORMA-02, and the evaluation of the application did not identify unexpected and/or significant safety issues.
- o The clinical study design was acceptable, and did not raise substantial review issues.
- o FRT with FC is an accepted practice in the treatment of bleeding and perioperative management in CFD.

5.4.2 External Consults/Collaborations

There were no external consults/collaborations needed during this review.

5.5 Literature Reviewed (if applicable)

Not applicable.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: FORMA 01

A prospective, controlled, randomized, crossover study investigating the pharmacokinetic properties, surrogate efficacy and safety of Fibryna¹¹ compared to Haemocomplettan® P/RiaSTAP™ in patients with congenital fibrinogen deficiency

6.1.1 Objectives

Primary

- To determine the single-dose PK parameters of Fibryna and RiaSTAP in patients with congenital fibrinogen deficiency

¹¹ Octafibrin was a preliminary name for Fibryna and is the term used by the applicant in this BLA.

- To determine Maximum Clot Firmness (MCF) as a surrogate marker for hemostatic efficacy before and after administration of Fibryna and RiaSTAP in patients with congenital fibrinogen deficiency

Secondary

To assess the safety of Fibryna in patients with congenital fibrinogen deficiency

6.1.2 Design Overview

Subjects ≥ 12 years of age with afibrinogenemia were enrolled in this prospective, randomized crossover study, and were randomly assigned to receive Fibryna or the comparator RiaSTAP. Following a washout period of ≥ 45 days (maximum 45 days + 4 weeks) subjects received the alternate product.

6.1.3 Population

Inclusion criteria

- Age ≥ 12 years
- Documented congenital afibrinogenemia (plasma fibrinogen activity and antigen below limit of detection [$< 20\text{mg/dL}$])

Key exclusion criteria

- Dysfibrinogenemia
- Treatment with any fibrinogen-containing product within 2 weeks
- Current or history of hypersensitivity to study medication or human plasma proteins
- Arterial/venous thrombosis within 1 year
- Acute bleeding
- Liver disease (Child-Pugh B or C); history of bleeding esophageal varices
- Pregnancy or intention to become pregnant during the study/currently breastfeeding
- HIV with viral load > 200 particles per μL or 400,000 copies per mL
- Multiple trauma within 1 year
- Suspicion of anti-fibrinogen inhibitors

Reviewer comments: Subjects who were at risk from FRT, such as prior history of arterial or venous thrombosis or prior hypersensitivity reactions to fibrinogen, were excluded. These exclusions limit the external validity of the thrombotic risks as assessed in this study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects received infusions of 70 mg/kg of Fibryna and RiaSTAP at a rate of ≤ 5 mL/min in accordance with the crossover study design. No other medicinal products were used. Subjects were assigned to the two groups in a randomized ratio of 1:1 via a computer-generated schedule. The dose was selected based on an estimation that an IVR of 1.5 to

1.7% per IU per kg would result in a plasma level of 100 mg/dL, allowing for both PK assessment and a measurable increase in MCF, based on a recently published study of RiaSTAP.¹²

6.1.5 Directions for Use

Single infusions of 70 mg/kg of Fibryna and of the comparator, RiaSTAP. Fibryna was provided as a lyophilized powder and reconstituted in Sterile Water for Injection.

6.1.6 Sites and Centers

Bulgaria (1), India (3), Iran (2), Switzerland (1), United Kingdom (1), United States (2)

6.1.7 Surveillance/Monitoring

All trial-related source data/records were reviewed by one of several contract research organizations in the various countries to verify the adherence to the study protocol and the completeness, correctness and accuracy of all Case Report Form entries compared to source data.

Subjects were followed for 45 days after each infusion. Viral studies were done at day 45 (Parvovirus B19 on day 10). Adverse events (AE) were recorded actively in diaries and were solicited by questioning at study visits through day 14 after each infusion.

The study evaluations are shown below in Table 1.

Table 1. Scheduled Study Assessments

¹² Manco-Johnson MJ, Dimichele D, Castaman G, *et al.* Pharmacokinetics and safety of fibrinogen concentrate. *J Thromb Haemost* 2009; 7: 2064-9.

Dose: 70 mg/kg BW each		Eligibility/Informed consent	Medical History	Physical examination	Weight and height	Vital signs	Pregnancy test	Blood sampling:	MCF	Fibrinogen (PK)	Thrombogenicity ¹	Virus safety ²	Retain sample	Haematology ³	Biochemistry ⁴	Recording of AEs ¹²	
Time relative to end of infusion																	
Screening ⁵		x	x		x	x	x	Laboratory									
								Central ⁵						Local			
Study periods 1 and 2	Day 1	Before first infusion			x	X ₁ ¹	x		x	X ₇	x	x	x	x	x	x	
		0.5 hours					x			x	x						x
		1 hour					x		x	x	x				x	x	x
		2 hours					x		x	x							x
		4 hours							x	x							x
		8 hours							x	x							x
	Day 2	24 hours							x						x	x	x
	Day 3	48 hours							x								x
	Day 5	96 hours							x						x	x	x
	Day 7	144 hours							x								x
	Day 10	216 hours							x			x ⁸	x				x
	Day 14	312 hours			x		x		x		x ¹⁰				x	x	x
	Day 45	44 days ⁹											x	x			x

¹ Assessments included prothrombin fragment 1 + prothrombin fragment 2 and D-dimer.

² Assessments included (unless otherwise specified for the specific time point) HIV-1 and -2, HAV, HBV, HCV, and parvovirus B19.

³ Assessments included platelet count, haemoglobin, and haematocrit.

⁴ Assessments included AST, ALT, GGT, alkaline phosphatase, bilirubin total, creatinine, urea, potassium, sodium, calcium, and chloride.

⁵ See Section 6.2 for contact information for the central laboratories.

⁶ Study eligibility at screening was assessed via plasma level of fibrinogen measured at the central laboratory by the (b) (4) assay. If a patient is known to be HIV positive, the viral load assessment was performed locally.

⁷ Baseline fibrinogen for PK analysis (fibrinogen activity and antigen) was to be collected immediately prior to infusion of study drug.

⁸ Virus safety at this time point includes only (b) (4) of parvovirus B19.

⁹ Virus safety includes anti-HIV-1/HIV-2, anti-HAV antibodies and (b) (4) analysis for HAV, HBV, HCV, and HIV-1.

¹⁰ Clinical evaluation of TEE.

¹¹ Weight only.

¹² Including early signs of allergic or hypersensitivity reactions for the first 2 days following any treatment with study medication.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BW = body weight; (b) (4); GGT = Gamma-glutamyl transpeptidase;

HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MCF = maximum clot firmness; (b) (4)

PK = pharmacokinetic; SAE = serious adverse event; TEE = thromboembolic events.

Source: Study Report FORMA 01, Figure 3, page 24 of 677.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoints

- Ratio of AUC_{norm} for Fibryna:RiaSTAP lies between 80% and 125%
- Comparison of mean changes in MCF between Fibryna and RiaSTAP between baseline and the 1-hour value

PK analyses and MCF (by Rotem) were performed at a central laboratory.

Secondary Endpoints

PK analyses were the comparisons of PK variables of Fibryna and RiaSTAP. For each variable, the 90% CI was established.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Null hypothesis: H_0 : $\text{Ratio}_{\text{AUC}_{\text{norm}}} < 0.8$ or $\text{Ratio}_{\text{AUC}_{\text{norm}}} > 1.25$

An ANOVA model was assumed: $\text{Log}(\text{AUC}_{\text{norm}}) = \text{treatment effect} + \text{period effect} + \text{patient effect} + \text{error}$, with independence and normal distribution assumed.

The number of subjects was limited by the very small number of patients with this disorder and no sample size estimation was provided. Instead, the power of test procedures for a total number of 18 patients was determined for testing bioequivalence of AUC as described in the Statistical Analysis Plan (Appendix 16.1.9).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

- Safety: All randomized subjects who received ≥ 1 infusion of study medication

Reviewer comments: The safety analysis population as defined is acceptable.

6.1.10.1.1 Demographics

Demographics of this small subject group are shown in Table 2.

Table 2. Demographics

Parameter	Number of Subjects (%)
Sex:	
Female	15 (68)
Male	7 (32)
Age:	
12 to <18 years	6 (27)
18 to 53 years	16 (73)
Race:	
Asian	8 (36)
White	14 (64)
Ethnicity:	
Non-Hispanic/Latino	22 (100)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects had congenital afibrinogenemia.

6.1.10.1.3 Subject Disposition

Protocol deviations were noted that relate to the evaluation of the efficacy endpoints. For the safety analysis population, no deviations were noted. All of the 22 subjects who received the infusions are included in the safety analysis and none of these subjects discontinued the study prematurely.

6.1.11 Efficacy Analyses

For details of the discussion of the primary analysis as related to PK and PD endpoints, please refer to the Clinical Pharmacology review memo. The analysis of the IVR was a secondary analysis in the study. As part of the IVR evaluation, mean fibrinogen levels at 1 hour were recorded. The mean fibrinogen levels following the administration pre-infusion and 1 hour post infusion was available for 19 of the 22 subjects who were dosed at 70mg/kg. The mean levels pre-infusion were 0 mg/dL and 125 mg/dL 1 hour post-infusion.

The reviewer concludes that in these subjects with congenital afibrinogenemia (as noted by the mean pre-infusion levels of 0 mg/dL) the dose of 70mg/kg is likely to achieve a target fibrinogen level that is >100mg/dL (a level that is sufficient to achieve hemostasis in acute bleeding as recommended in the UK Guidelines). Thus, the mean fibrinogen levels noted 1 hour post infusion is supportive of the proposed dosing recommendations for the 70mg/kg dose for treatment of patients for whom the pre-treatment fibrinogen levels are unavailable.

6.1.12 Safety Analyses

The safety population consisted of all 22 enrolled patients who received a total of 22 infusions of Fibryna and 22 infusions of RiaSTAP. Eleven subjects (50%) developed a total of 25 AEs during (within 14 days) or after (14 to 45 days) receiving Fibryna.

6.1.12.1 Methods

Physical examinations were performed before drug infusion and on day 14 for each study period. Safety laboratory tests¹³ were obtained before infusion, at 1 hour and on days two and 14. Tests of thrombogenicity (prothrombin fragments 1 and 2 and D-dimer) were measured before drug infusion and at 0.5, 1, 2, 4 and 8 hours. Any reported event was considered an AE. Viral testing for multiple viruses was done at day 45 of each treatment study period. All AEs were noted at study visits and entered into the Case Report Form. Treatment emergent AEs (TEAEs) were those occurring during infusion or in the 44 days observation period after each treatment.

Safety data were categorized using MedDRA version 18.0.

¹³ Platelet count, hemoglobin, hematocrit; ALT, AST, CGT, alkaline phosphatase, bilirubin total, creatinine, urea; serum electrolytes (sodium, potassium, bicarbonate, calcium).

6.1.12.2 Overview of Adverse Events

There were 39 TEAEs reported in 11 subjects:

- 17 TEAEs (14 mild, two moderate and one severe) in 9 subjects (41%) during the Fibryna treatment period
 - One severe TEAE of urinary tract infection was assessed by the applicant as unrelated. Reviewer concurs.
 - One mild TEAE of pyrexia, was assessed by the investigator as possibly related.
- 22 (21 mild, one moderate) in 9 subjects (41%) during the RiaSTAP treatment period.

There were 16 late (“post”) TEAEs in 9 subjects, occurring from days 15 to 45 of each study period. Eight of these, (one mild, seven moderate) occurred in the Fibryna treatment period and eight in 7 subjects (five mild and three moderate) during the RiaSTAP treatment period.

Overall there were 25 TEAEs and post-TEAEs (17 TEAEs and 8 post TEAEs as described above) reported in 11 subjects during the Fibryna treatment period and 30 in 11 subjects during the RiaSTAP treatment period. TEAEs for Fibryna are summarized below in Table 2.

Table 2: TEAEs occurring during the Fibryna treatment period by System Organ Class and Preferred Term (Safety Population, N=22)

TEAEs by Organ System	Preferred Term	N(%) of events 17 (41)
Gastrointestinal	Abdominal pain	1(4.5)
	Diarrhea	1(4.5)
	Dyspepsia	1(4.5)
	Gingival Bleeding	1(4.5)
	Decreased appetite	1 (4.5)
Constitutional	Asthenia	1(4.5)
	Pyrexia	1(4.5)
Respiratory	Cough	1(4.5)
	Pharyngitis	1(4.5)
Genitourinary	Urinary Tract Infection	1(4.5)
Musculoskeletal	Arthralgia	1(4.5)
Injury	Fall	1(4.5)
	Contusion	1(4.5)
Nervous system	Dizziness	1(4.5)
Vascular	Bleeding (vaginal)	1(4.5)
	Anemia	1(4.5)
	Thrombophlebitis	1(4.5)

Source: Adapted from Table 27, pages 67 to 68 of 677, Study Report FORMA-01

6.1.12.3 Deaths

No deaths were reported.

6.1.12.4 Nonfatal Serious Adverse Events

There was one Serious Adverse Event reported: vaginal bleeding and abdominal pain. Subject (b) (6) developed vaginal bleeding and abdominal pain that required hospitalization for 3 days. Resolution occurred without complications. The reviewer considers this event to be unrelated to Fibryna, but rather a manifestation of the underlying disease.

6.1.12.5 Adverse Events of Special Interest (AESI)

AESI of interest were events that were considered by the reviewer as being related and specific to Fibryna.

Pyrexia and thrombophlebitis: Subject (b) (6) developed mild pyrexia and thrombophlebitis lasting eight days that resolved subsequently. This event is considered expected but related to the administration of Fibryna.

Anemia: Subject (b) (6) was noted to have mild anemia prior to study treatments, noted to have Hb 13 g/dL prior to Fibryna that remained stable 14 days after treatment. Therefore, the anemia is not considered related to Fibryna.

There was no case of viral conversion. A single subject with absorbance values near the border of positivity for hepatitis A virus had several values both positive and negative, and hepatitis A virus RNA was not detected.

6.1.12.7 Dropouts and/or Discontinuations

No subject withdrew from the trial.

6.1.13 Study Summary and Conclusions

Efficacy

Please refer to the Clinical Pharmacology review memo for primary efficacy assessments that relate to PK and PD endpoints. As discussed in 6.1.11, the reviewer concludes that the mean fibrinogen levels noted in 19 of 22 subjects, 1 hour post infusion is supportive of the proposed dosing recommendations in the label for the 70mg/kg dose for treatment of patients with congenital afibrinogenemia.

Safety:

- The incidence, type and quality of most TEAEs and all AEs were mild following RiaSTAP and Fibryna.
- One subject had two serious TEAEs (vaginal bleeding and pain), assessed by the reviewer as unrelated to treatment

- There were no deaths or premature discontinuations from the study.
- There was no viral seroconversion.
- This reviewer assessed TEAEs of pyrexia and thrombophlebitis as possibly related to study drug and expected.

Thus, the data from the FORMA 01 study suggests that the adverse events attributable to Fibryna are mild.

6.2 Trial #2: FORMA 02

Trial #2 (FORMA 02) is an ongoing, prospective, open-label, uncontrolled, phase 3 study to assess the efficacy and safety of Fibryna for on-demand treatment of acute bleeding and perioperative management subjects with congenital fibrinogen deficiency. A total of 24 subjects are to be enrolled. An interim analysis for efficacy was conducted after 10 subjects experienced bleeding.

6.2.1 Objectives

Primary

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

Secondary

- To demonstrate the efficacy of Fibryna in preventing bleeding during and after surgery.
- To show an association between the overall clinical assessment of hemostatic efficacy and the surrogate endpoint MCF
- To achieve a peak target plasma fibrinogen level of 100 mg/dL in minor bleeds and 150 mg/dL for major bleeds 1 hour post-infusion.
- To determine the response to Fibryna based on incremental IVR.
- To assess the safety of Fibryna in subjects with congenital fibrinogen deficiency, including immunogenicity, thromboembolic complications, and early signs of allergic or hypersensitivity reactions.

6.2.2 Design Overview

This trial is not yet complete. This submission includes an interim analysis of efficacy related to hemostatic control from ≥ 10 subjects. Therefore, this submission is acceptable as it meets the FDA request on August 24, 2011 to provide efficacy data based on hemostatic control since MCF had not been validated. Two subjects between 12 and 18 years of age, were included in the efficacy analyses to evaluate the efficacy in adolescent subjects.

In this multicenter, multinational, phase 3, open-label, uncontrolled trial, the hemostatic efficacy of Fibryna was assessed in subjects with acute BE or for perioperative prophylaxis. Subjects were given Fibryna individually dosed to achieve a target fibrinogen plasma level of 150 mg/dL for major bleeding or major surgery or 100 mg/mL for minor bleeding or surgery.

Reviewer comments: The target plasma fibrinogen level of 150 mg/dL for management of major surgery and major bleeding are higher than levels generally used of 100 mg/dL in clinical practice for FRT.

6.2.3 Population

Key inclusion criteria

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

Key exclusion criteria

- Bleeding disorder other than afibrinogenemia, including dysfibrinogenemia
- Treatment with any fibrinogen-containing product within 2 weeks
- Any coagulation-active drug within 1 week before start of treatment for BE or surgery or before 24 hours after the last Fibryna infusion.
- Hypersensitivity to study medication or plasma proteins
- Deep vein thrombosis or pulmonary embolus within 1 year
- Arterial thrombosis within 1 year
- Bleeding esophageal varices
- Liver disease (Child-Pugh B or C)
- Pregnancy within the first 2 weeks or currently breast-feeding
- Known HIV infection (viral load > 200 particles/ μ L)
- Multiple trauma within 1 year
- Diagnosed or suspicion of anti-fibrinogen inhibitor currently or in the past

Reviewer comments: Subjects at higher risk of thrombosis were excluded from the study thereby limiting the external validity of the safety data. Subjects with CFD are at risk for paradoxical thrombotic events (as discussed in the Disease Background section). Excluding such subjects in a trial where the risks of thrombosis from treatment may occur (as with FRT) suggests that the trial population may not be representative of the “real world” population, thereby limiting the interpretability of the safety data as related to risk of thrombosis.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Table 3: Treatment Plan by Indication

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

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

The dose was calculated individually based on the following formula:

$$\begin{aligned}
 & \text{Fibrinogen dose } \left(\frac{mg}{kg} \right) \\
 &= [Target \text{ peak plasma level } \left(\frac{mg}{dL} \right) - measured \text{ level } \left(\frac{mg}{dL} \right)] \\
 &\div Median \text{ response } \left(\frac{mg}{dL} \text{ per } \frac{mg}{kg} \right)
 \end{aligned}$$

Major Bleeding was defined as symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, retroperitoneal, intraarticular or pericardial, intramuscular bleeding with compartment syndrome, or bleeding causing a decrease in hemoglobin by at least 2 g/dL.

Minor Bleeding was defined as mild hemarthrosis, superficial muscle and soft tissue and oral bleeding.

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

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

Investigator discretion was allowed in classifying the type of surgery if the surgery was not identified in the above mentioned list.

Concomitant Medications

- Permitted Medications: Rescue therapy was permitted at the investigator's discretion and included the option of RiaSTAP.
- Forbidden Medications: Non-steroidal anti-inflammatory drugs, warfarin, coumarin derivatives, platelet aggregation inhibitors were not permitted within 24 hours of Fibryna infusion, up to 1 week prior to surgery and treatment of bleeding episodes.

6.2.5 Directions for Use

See section 6.2.4. Fibryna was administered as a bolus infusion at a rate not exceeding 5 mL/min.

Preparation of the product for administration

The vial of Fibryna was reconstituted with 50 ml of sterile water for injection (SWI). Room temperature was to be maintained during reconstitution. The product was expected to dissolve in the SWI within 30 minutes producing a colorless or opalescent solution. If the solution appeared cloudy or with particulate material, it was not to be administered.

Reviewer comment: The protocol and study report do not mention use of the Octajet device or filter with the reconstitution of the product. However, the Applicant proposes to market the Octajet device and filter for reconstitution of the product. The device and filter will be packaged with the vial of Fibryna in a single carton. The review of the data related to the device was conducted by the CMC reviewers in CBER and device reviewers in the Center for Diagnostic and Radiological Health.

6.2.6 Sites and Centers

United States (1), United Kingdom (2), Bulgaria (1), Turkey (1), Saudi Arabia (1), Lebanon (1), Russia (1), India (3), Iran (2)

6.2.7 Surveillance/Monitoring

Assessments for on-demand treatment for acute bleeding are shown in [Appendix 1](#), and for perioperative prophylaxis in Appendix 2.

6.2.8 Endpoints and Criteria for Study Success

Efficacy

1. Primary:

Hemostatic efficacy: Success was based on the investigator's clinical assessment of hemostatic activity in treating the first documented BE for each subject using a four point

rating scale, as discussed in section 6.2.11. Success was defined as a rating of “excellent” or “good”.

2. Key Clinical Secondary Endpoints:
 - a. Fibrinogen plasma level before and 1 hour after the end of each subsequent infusion as well as at the time of the overall clinical assessment of hemostatic efficacy (i.e. at 24 hours) after treatment of BE episode)
 - b. Efficacy in all bleeding episodes using the overall clinical assessment of hemostatic efficacy based on a 4-point hemostatic efficacy scale
 - c. Efficacy of Fibryna in preventing bleeding during and after surgery as assessed at the end of surgery by the surgeon and post-operatively by the hematologist using two 4-point hemostatic efficacy scales.
3. Key Secondary Pharmacokinetic and Pharmacodynamic Endpoints:
 - a. IVR
 - b. MCF assessment baseline and 1 hour post infusion.
4. Key Safety Endpoints:
 - a. Thrombogenic complications
 - b. Allergic or hypersensitivity reactions following treatment administration
 - c. Immunogenicity assessments as performed on days 14 and 30 days following the infusion of Fibryna

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

6.2.9 Statistical Considerations & Statistical Analysis Plan

The planned 90% CI for both the primary efficacy analysis (efficacy for the first bleeding episode), and the secondary efficacy analysis (efficacy for all bleeding episodes).

The tested hypothesis for the primary efficacy analysis was:

$H_0: p \leq 0.7$ against the alternative $H_A: p > 0.7$

Where p is the proportion of subjects with hemostatic success (i.e. rating of excellent or good) and the null hypothesis was tested by comparing the lower limit of the two-sided CI (see section 6.2.9).

Missing data were not imputed or interpolated (graphs).

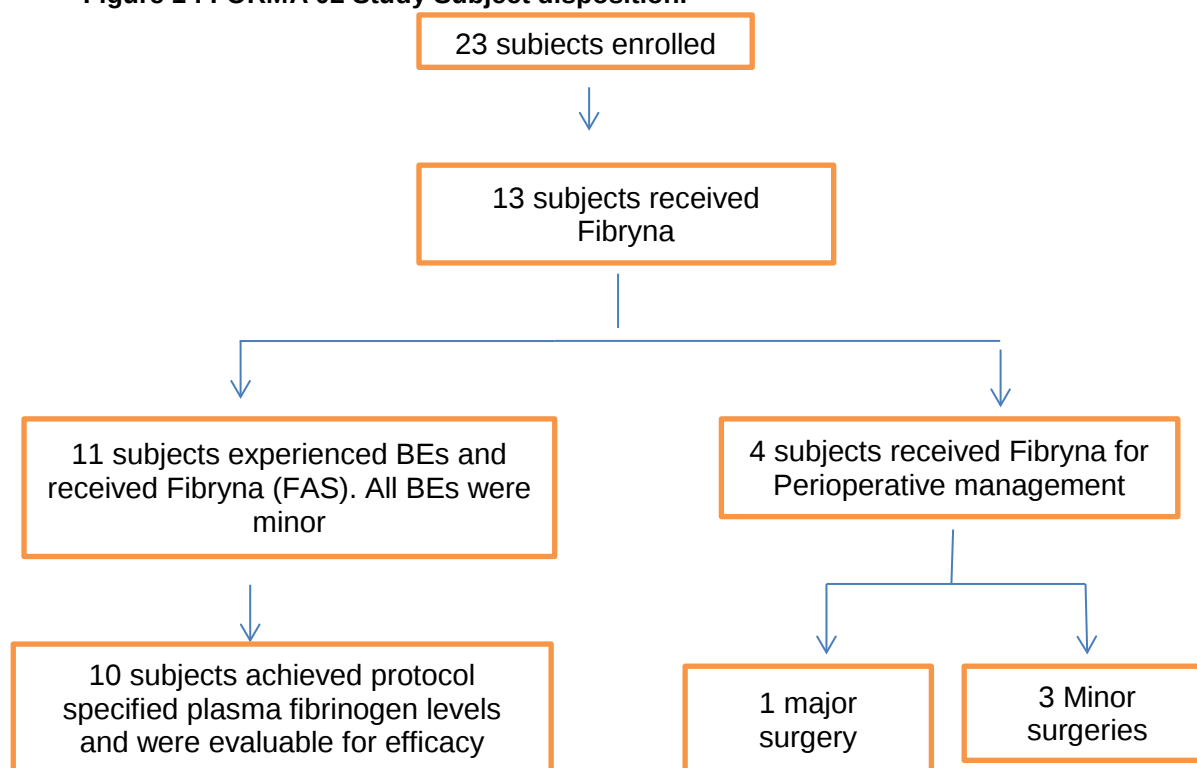
Reviewer note: The clinical efficacy data from the only available FC product in the United States is pending completion of the confirmatory study for RiaSTAP. To

evaluate whether the boundaries set forth for the alternate hypothesis were clinically meaningful, the reviewer evaluated the hemostatic efficacy of CLOTTAFAC[®] another plasma derived FC product that is a marketed product outside the United States. The hemostatic control data available in the published literature is discussed below. There were two interventional prospective studies of FibCLOT (CLOTTAFAC[®]) a fibrinogen concentrate licensed in France conducted to evaluate the efficacy of hemostasis. In Study 41-67-113, 20 of 21 (95%) bleeding episodes were treated successfully in four of six subjects with congenital afibrinogenemia, with success defined as excellent and good on a 4 point scale. In Study FGT1-A616, 16 of the enrolled 20 (19 subjects with congenital afibrinogenemia) subjects were evaluated for hemostatic efficacy in acute bleeding and in the perioperative setting. A total of 15 of 38 (40%) surgical procedures were considered to have successful hemostasis and 9 of 32 (28%) bleeding episodes were treated successfully. Therefore, the study success criterion based on an alternate hypothesis of $p > 0.7$ as proposed in the FORMA 02 study, for the treatment of bleeding and perioperative management is reasonable.

6.2.10 Study Population and Disposition

Figure 1 below outlines the disposition of subjects in the arms that enrolled subjects for treatments of perioperative and acute bleeding episodes.

Figure 1 : FORMA 02 Study Subject disposition.



The primary population was the Full Analysis Set (FAS). Please see Section 6.2.10.1 below for the definition of FAS. The following subjects were excluded from the FAS.

- Subject (b) (6), a 42 year old male, was excluded from the FAS-bleeding population as he had no BE. He was included in the FAS-surgery population.
- Subject (b) (6), a 19 year old male, was excluded from the FAS-bleeding population as he had no BE. He was included in the FAS-surgery population.

The reviewer agrees with exclusion of the two subjects from the analysis of hemostatic efficacy for first (primary endpoint) and all bleeding episodes (secondary endpoint).

6.2.10.1 Populations Enrolled/Analyzed

- Safety population
 - All subjects who received at least one infusion of Fibryna
- Full analysis set (FAS) – defined according to intention to treat. All subjects who met all of the following criteria:
 - Received at least one infusion of Fibryna.
 - Entered the study with a confirmed congenital fibrinogen deficiency.
 - Presented with an episode of acute bleeding or underwent a surgical procedure with a need for at least one infusion of Fibryna.
- Two subpopulations: FAS-bleeding (treated for BE) and FAS-surgery
- Efficacy per-protocol(PP) population – all subjects in the FAS population who met the following criteria:
 - Provided valid, non-missing hemostatic efficacy data.
 - Provided a 1-hour post-infusion MCF value.
 - Received $\geq 90\%$ of the planned total dose of Fibryna in the first infusion.
 - Received $\geq 80\%$ of the calculated dose of Fibryna during further infusions according to the treatment schedule
 - Did not meet any exclusion criteria

6.2.10.1.1 Demographics

Demographic information on the safety population is shown in the Table 14.

Table 4: Demographic Information

Parameter	Subjects treated for BE (n=11) N (%)	Subjects treated for Surgery (n=4)
Gender		
Male	5 (54)	2 (50%)
Female	6 (46)	2 (50%)
Race		
White	9 (69)	2 (50%)
Asian	3 (23)	1 (25%)
Other (Arab/Middle Eastern)	1 (8)	1 (25%)
Ethnicity		

Hispanic/Latino	1 (8)	
Age		
12 to <18 years old	2 (16)	0
≥18 years old	11 (84)	4 (100%)
Fibrinogen Deficiency±		
Afibrinogenemia*	5 (45)	
Hypofibrinogenemia+	5 (45)	
Fibrinogen levels >50mg/dL	1(9)	
Annualized Bleeding Rate (Median/Mean)	4/6.3	2/2.5

±All 11 subjects in the BE subgroup met the enrollment criterion for fibrinogen deficiency based on the documented history of congenital fibrinogen deficiency. However, one subject was noted to have a baseline fibrinogen level of 60mg/dL following enrollment and prior to the first dose of Fibryna. The subject was included in the FAS set.

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

- Median ages for subjects treated for BE was 28 years and subjects who underwent perioperative prophylaxis was 41 years. Two of the adolescent subjects treated for BE were 14 and 13 years of age.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Ten subjects had one or more relevant medical problems, three subjects had prior intracranial hemorrhage.

Reviewer comment: The inclusion of subjects with underlying hemorrhagic risks from prior events is representative of the CFD population. The prior history of ICH did not impact the interpretability of the efficacy results.

6.2.10.1.3 Subject Disposition/Protocol Deviations

Subject disposition is shown in Figure 1. Note that two subjects treated for BE also had surgical procedures, thus the safety population = 13 subjects but the FAS-bleeding + FAS surgery populations = 15 subjects.

Of the 31 protocol deviations related to the treatment of bleeding episodes, 18 were related to Subject (b) (6). There were 4 protocol deviations related to perioperative management of the 4 subjects of which two were related to Subject (b) (6) and two were Subject (b) (6).

Two major deviations observed were related to dosing:

- Subject (b) (6) was administered approximately half the planned dose on the day of infusion and received the remainder of the dose the following day.
- Subject (b) (6) received approximately half the planned dose

The minor protocol deviations were noted and related to assessment of vital signs or missing laboratory values

Reviewer comment: The major protocol deviations relate to “under dosing”. Both subjects were considered to have excellent hemostasis by the clinical reviewer and IDMEAC. However, Subject (b) (6) was excluded from the FAS set by the clinical reviewer since the post-infusion fibrinogen levels were unchanged (10mg/dL) from the baseline.

6.2.11 Efficacy Analyses

Hemostatic activity of Fibryna was assessed for the first BE only (see Advice/information request letter, April 14, 2016, discussed in section 2.5). The rationale for this criteria in the primary efficacy analysis was to minimize the potentially undue influence on overall results from a few patients with multiple BE. Hemostatic efficacy for all BEs was considered as a secondary endpoint.

Table 5: Four point scales for assessment of hemostatic efficacy for Bleeding Events, Surgery and Post-operative bleeding

Category	Bleeding Event	Intraoperative	Post-operative
Excellent	Immediate and complete cessation of bleeding in the absence of other hemostatic intervention as clinically assessed by the treating physician; and/or <10% drop in haemoglobin compared to pre-infusion.	Intra-operative blood loss* was lower than or equal to the average expected blood loss for the type of procedure performed in a subject with normal hemostasis and of the same sex, age, and stature.	No post-operative bleeding or oozing that was not due to complications of surgery. All post-operative bleeding (due to complications of surgery) was controlled with <i>Fibryna</i> as anticipated for the type of procedure.
Good	Eventual complete cessation of bleeding in the absence of other hemostatic intervention as clinically assessed by the treating physician; and/or <20% drop in haemoglobin compared to pre-infusion.	Intra-operative blood loss* was higher than average expected blood loss but lower or equal to the maximal expected blood loss for the type of procedure in a subject with normal hemostasis.	No post-operative bleeding or oozing that was not due to complications of surgery. Control of post-operative bleeding due to complications of surgery required increased dosing with <i>Fibryna</i> or additional infusions, not originally anticipated for the type of procedure.
Moderate	Incomplete cessation of bleeding and additional hemostatic intervention	Intra-operative blood loss* was higher than maximal expected blood loss for the type of procedure performed	Some post-operative bleeding and oozing that was not due to complications of

Category	Bleeding Event	Intraoperative	Post-operative
	required, as clinically assessed by the treating physician; and/or between 20 and 25% drop in haemoglobin compared to pre-infusion.	in a subject with normal hemostasis, but hemostasis was controlled.	surgery; control of post-operative bleeding required increased dosing with <i>Fibryna</i> or additional infusions, not originally anticipated for the type of procedure.
None	No cessation of bleeding and alternative hemostatic intervention required, as clinically assessed by the treating physician; and/or >25% drop in haemoglobin	Hemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.	Extensive uncontrolled post-operative bleeding and oozing. Control of postoperative bleeding required use of an alternate fibrinogen concentrate.

Reviewer comment: The four point scale for hemostatic efficacy in BE has been utilized to assess efficacy for regulatory review of assessment of efficacy outcomes for products that treat coagulation disorders. The limitations of the scale relate to the subjectivity in assessments by the investigator. For example, assessment of cessation of bleeding in soft tissues is measured by pain and in some cases the range of motion. In minor bleeding, it is difficult to elicit substantial improvement in pain and range of motion that is clinically relevant as the clinical findings may not be associated with severe pain. In addition, there are limitations to the relevance of a drop in hemoglobin to minor bleeding. A drop in hemoglobin is unlikely to be detected with minor bleeding. For these reasons, inclusion of major bleeding and its outcomes are relevant to a robust assessment of hemostatic outcomes when the four point scale is utilized.

Table 6: Adjudication algorithm for hemostatic efficacy for perioperative management of bleeding

Intra-operative assessment	Post-operative assessment			
	Excellent	Good	Moderate	None
Excellent	Success	Success	Success	Primary Adjudication
Good	Success	Success	Primary Adjudication	Failure
Moderate	Success	Primary Adjudication	Failure	Failure
None	Primary Adjudication	Failure	Failure	Failure

The final efficacy assessment for each subject was adjudicated by the Independent Data Monitoring and Endpoint Adjudication Committee (IDMEAC).

In addition, MCF, as in study FORMA 01, was measured before the first infusion and 1 hour after the end of the first and last infusion.

6.2.11.1 Analyses of Primary Endpoint(s)

Hemostatic Efficacy in On-Demand Treatment of First BE

All of the first BEs were assessed as minor. Eight (73%) were spontaneous and three (27%) were traumatic. Nine subjects received only a single infusion of Fibryna and two subjects received two infusions. One of the two subjects who received the second infusion did so two days after the bleeding event and was confirmed to have excellent hemostatic control 24 hours post infusion.

The median and mean doses of the first dose of Fibryna administered for treatment of all subjects were 57.5mg/kg and 57mg/kg respectively. The median and mean dose of plasma fibrinogen levels one hour post infusion for the first bleeding event in subjects who received the protocol specified dose was 120 mg/dL and 122 mg/dL (89-173 mg/dL).

Per the Applicant, the FAS-bleeding population (n=11) (one treatment with Fibryna was successful for the first bleeding episodes in all subjects in the study. Efficacy of Fibryna was rated as excellent for 9 (82%) and as good for 2 (18%) of the first bleeding episodes by the investigator (95% CI 0.75 to 1.0). The IDMEAC rated efficacy of all first bleeding episodes as excellent (95% CI 0.75 to 1.0). Thus, per the applicant the criterion for success (rating of excellent or good) was met for 100% of subjects, as assessed by both investigators and the IDMEAC. The lower CI limit for the rate of successfully treated first bleeding episodes was greater than 70% for the first BE, meeting the a priori success criterion for the primary endpoint.

Reviewer's comments: The reviewer's primary efficacy analysis differs from the Applicant in that one subject with major protocol deviation was excluded from the efficacy analysis population. Two subjects were considered by the reviewer as subject to major protocol deviations related to dose. Subject (b) (6) and Subject (b) (6) received lower than the protocol specified dose for their first bleeding episode with resultant post infusion fibrinogen levels <10 md/dL and 141 mg/dL respectively. Both subjects achieved excellent hemostasis despite abnormal fibrinogen levels. As is anticipated in bleeding episodes in congenital fibrinogen deficiency, spontaneous hemostasis may occur without replacement therapy. The testing of the alternate hypothesis rests on a lower limit of CI of greater than 70% which assumes that hemostatic efficacy may be achieved for hemostatic control for reasons other than the intervention. This subject's hemostatic outcomes likely represents the results of an alternate plausibility other than the treatment intervention and is evidenced by the fibrinogen levels that were unchanged from

baseline and at 1 and 3 hours post-infusion. Therefore, the subject's hemostatic outcome was considered not attributable to Fibryna. Subject (b) (6) on the other hand achieved target fibrinogen levels despite the lower dose. Therefore, in this subject the efficacy outcome associated with the post infusion target fibrinogen levels is likely to have contributed to hemostatic outcomes. The primary efficacy analysis was performed by excluding the subject ((b) (6)) from the FAS population resulting in 10 evaluable subjects, all of whom (100%) achieved successful hemostatic outcomes. Since the hypothesis testing was not designed to evaluate the impact of fibrinogen levels on hemostatic outcomes, the best approach in the reviewer's opinion is to exclude the subject from the efficacy evaluable population. The 90% lower bound of the CI levels was 0.78 by the protocol specified Blyth Still Casella method. Therefore the study met the pre-specified success criteria for efficacy in subjects who were treated for the first BE. Per the sensitivity analyses, the point estimate of 91% with a lower limit of 90% CI of 0.65 by the protocol specified Blyth Still Casella method was observed. Therefore, the primary efficacy outcomes were not supported by this sensitivity analysis. Nevertheless, based on the protocol specified primary analysis, the primary reviewer concludes that the success criteria based on the primary efficacy analyses was reached. The reviewer suggests that for the final analysis planned in the future after enrollment of 25 subjects, the efficacy evaluable population is revised to only include those subjects that achieve the protocol specified "acceptable post-infusion minimum target fibrinogen level". The reviewer further recommends that the protocol is revised to include a secondary efficacy analysis to evaluate the percentage of subjects who received the dose targeted to achieve a plasma fibrinogen level but did not achieve the "acceptable post-infusion minimum fibrinogen level".

The discrepancy in the IDMEAC and investigator reading for the two subjects is based on IDMEAC decision to include laboratory and absence of the need for a second infusion as being considered as meeting the criterion for excellent hemostasis. However such a definition is not considered a protocol definition of excellent and good hemostasis. Therefore, an information request was sent on February 6, 2017. The applicant's response confirmed that primary hemostatic outcomes were excellent for all subjects with missing information with the exception of Subject (b) (6) . For this subject, the CRF notes overall hemostatic efficacy as being successful by the investigator and IDMEAC without supportive evidence of physical exam findings reported for the bleeding site. Therefore for the purpose of the primary efficacy analysis the reviewer agrees with the IDMEAC's conclusion that this subject achieved excellent hemostasis. A sensitivity analysis was performed including this subject in the efficacy analysis population but considered to have failed treatment.

6.2.11.2 Analyses of Secondary Endpoints

Hemostatic efficacy in on-demand treatment of all BE

Ninety-one percent (20 of 22) of all BE required only a single infusion of Fibryna. The mean ($\pm$ SD) Fibryna dose per BE was 63.4 mg/kg ($\pm$ 16.0) and the median (range) was

60.6 mg/kg (33.9-101.7 mg/kg). The median and mean plasma fibrinogen levels achieved 1 hour post infusion in subjects who received the protocol specified dose were 112 mg/dL and 116 mg/dL (range 79-173 mg/dL).

Per the Applicant's report, 23 subjects were evaluable for efficacy for on demand treatment of all BE. Excellent hemostasis outcomes were noted in nineteen out of the 23 (82.6%), good in 3 (13.0%) and was missing in one subject, and thus considered a failure, for one (4.4%) bleeding episode by investigator. Efficacy in all 23 bleeding episodes was considered excellent by the IDMEAC. Thus the treatment was deemed successful in 22 of 23 (96%) of subjects by the investigators (95% CI 0.8 to 1.0) and 23 of 23 (100%) of subjects by the IDMEAC (95% CI 0.87 to 1.0)¹⁴. The lower CI limit for the rate of successfully treated bleeding episodes was greater than 70% for treating all BE.

Reviewer's comment: Discrepancies between the IDMEAC and investigator assessments were noted in three subjects. These discrepancies between the IDMEAC and investigators were due to differences in the definition of excellent hemostasis and deviation by the IDMEAC from the protocol specified definition. However, in two of these three subjects the response to the FDA IR request and additional information provided confirmed that these subjects achieved excellent hemostasis at 24 hours following the infusion. Subject (b) (6) as discussed in Section 6.2.11.1 was excluded from the secondary efficacy evaluable population. In addition for Subject (b) (6) the 9th bleeding episode had missing hemostatic efficacy assessments (resulting from the fall and subsequent injury). The final outcomes of the secondary analysis is consistent with the primary efficacy analysis, therefore additional sensitivity analyses were not performed. The median and mean plasma fibrinogen levels achieved 1 hour post infusion were below the protocol defined target plasma fibrinogen levels (lower limit of 130mg/dL and target level of 150mg/dL) for control of major bleeding but within the protocol defined acceptable range for treatment of minor bleeding. There is limited efficacy data for the dose required (dose to target plasma fibrinogen level of 150mg/dL) to treat major bleeding. Given the rarity of congenital fibrinogen deficiency, the efficacy data to support an indication in major bleeding is therefore based on the totality of data from a) the pharmacokinetic data from the FORMA 01 study, b) the mean plasma fibrinogen levels of 122 mg/dL (89-173 mg/dL) noted following treatment of 22 minor bleeding events and one perioperative prophylaxis treatment for major surgery in FORMA 02 and data from the published literature to support control of major bleeding at levels at or above 100mg/dL.

Hemostatic efficacy in perioperative prophylaxis

Four subjects (two of whom also were treated for BE) underwent one surgical procedure each. One surgery was major and the remainder were minor.

¹⁴ Subject # (b) (6) was treated for the 9th BE for that subject, a spontaneous minor BE in the right arm. That subject was observed for 4 hours after treatment with a stable hematocrit. The subject then fell and broke a patella. No local efficacy score required an investigator assessment of failure. The members of the IDMEAC unanimously and independently assessed it a successful.

- Subject # (b) (6), minor (radioisotope synovectomy of knee)
- Subject # (b) (6), minor (dental extraction, single tooth)
- Subject # (b) (6), minor (circumcision)
- Subject # (b) (6), major (right eye enucleation with socket reconstruction)

No subject required intraoperative dosing beyond the first dose. One minor procedure required one additional postoperative dose and the other required two postoperative doses. The subject with the major procedure required seven postoperative infusions.

- o Intraoperative treatment: Treatment was assessed as successful in all subjects (rating of excellent [3] or good [1], 95% CI 0.47 to 1.0). The surgeons and the IDMEAC agreed in all cases.
- o Postoperative assessment: The hematologists assessed the success as 100% of all four procedures (95% CI 0.47 to 1.0). The IDMEAC rated the efficacy as excellent for the three minor surgeries and good for the major surgery (the same success rate for rating of excellent or good).

Reviewer Note: Subject # (b) (6) was the only subject who underwent major surgery. As noted in the CRF the anticipated average blood loss for the surgery was 15 ml and the maximal blood loss was 100 ml and transfusions were not anticipated. The actual blood loss was 60 ml. Therefore the subject was noted to have good hemostasis per the protocol specified definition. (b) (4)



MCF for First BE

The assessment of the pharmacodynamics endpoint of change in MCF from baseline to post infusion, for the treatment of first BE and all BE's is being deferred to the Clinical Pharmacology reviewer.

Fibrinogen Plasma Concentrations for All Bleeding Episodes

Please refer to Section 6.2.11.1 and 6.2.11.2 for results.

6.2.11.3 Subpopulation Analyses

Hemostatic efficacy by sex subgroup

- o First BE: The treatment was successful for all subjects (N=6 females and N=5 males; 95% CI 0.60 to 1.0 for females and 0.50 to 1.0 for males).
- o All BE: There were 8 BE in 6 females and 15 BE in 7 males. Full data was missing on one male subject. The success rate in female subjects was 100% (95%

- CI 0.95 to 1.0). The rate of success in male subjects was 93.3% (95% CI 0.70 to 1.0) as assessed by the investigators. The IDMEAC assessed all as successes, with a 95% CI of 0.79 to 1.0.
- o Perioperative prophylaxis: Three procedures were in males and one in a female. For all four procedures intraoperative and postoperative treatment was assessed as successful (success 95% CI 0.05 to 1.0 for females and 0.37 to 1.0 for males).

Reviewer's comments: The results of hemostatic efficacy in both the primary efficacy and secondary efficacy BE sub-groups are comparable between both sexes but should be interpreted in the context of the sample sizes. (b) (4)

[REDACTED]

6.2.11.4 Dropouts and/or Discontinuations

No subjects discontinued prematurely because of an AE.

6.2.11.5 Exploratory and Post Hoc Analyses

None

6.2.12 Safety Analyses

All 13 treated subjects are included in the safety population. They received a total of 38 infusions of Fibryna, with a mean dose of 143 mg/kg. Sixteen AEs occurred in 7 (54%) subjects, of which 13 AEs in 7 subjects were TEAEs. Three AEs in 2 subjects were non-TEAEs.

6.2.12.1 Methods

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

As indicated, in the Pre-BLA meeting (CRMTS#10194), April 22, 2016, FDA requested a causality assessment of AEs by the applicant in addition to the investigators. As reported in the Addendum to FORMA 02, there was agreement for 100% of the AEs and serious adverse events (SAEs) between the investigators' causality assessment and the applicant's causality assessment.

Safety data were categorized using MedDRA version 18.1.

Severity of the AE was categorized as:

- Mild: transient and causes discomfort but does not interfere with the subject's routine activities.

- Moderate: sufficiently discomforting to interfere with the subject's routine activities
- Severe: Incapacitating and prevents pursuit of subject's routine activities

6.2.12.2 Overview of Adverse Events

AEs (which include TEAEs) are summarized in Table 19.

Table 7: Summary of Severity of all AEs (Safety Population, N=13)

Severity Type	Number	Relatedness to Fibryna
Severe	2	Not related
Moderate	1	Not related
Mild	13	12 Not related; 1 possibly related

Reviewer's comment: The two AE reported as serious occurred in Subject (b) (6). This subject experienced patellar fracture and ligament rupture following a fall one day after the infusion of Fibryna and required hospitalization and surgery. This event is considered unrelated by this reviewer. The subject received Hemocomplettan® for perioperative management of the patellar fracture and ligament rupture and therefore was not included in the surgery study for Fibryna. The single AE of moderate severity was related to a wasp sting of the tongue and therefore considered unrelated.

Table 8: Summary of Mild AEs

Subject ID	Type	Severity	Relation to Fibryna	Date of onset from the infusion day	Date of resolution from the infusion day
(b) (6)	Gingival bleeding	Mild	Not related	32	32
	Haemorrhage	Mild	Not related	16	16
	Pain in extremity	Mild	Not related	283	283
	Pain in extremity	Mild	Not related	284	284
	Vomiting	Mild	Not related	272	272
	Vomiting	Mild	Not related	273	273
	Drug eruption	Mild	Likely related	1	1
	Drug	Mild	Not related	9	9

Subject ID	Type	Severity	Relation to Fibryna	Date of onset from the infusion day	Date of resolution from the infusion day
	eruption				
(b) (6)	Constipation	Mild	Not related	3	5
	Incision site pain	Mild	Not related	2	7
	Vomiting	Mild	Not related	1	2
	Asthenia	Mild	Not related	14	30
	Pharyngitis	Mild	Not related	3	6

Derived from Data Table AE.XPT in the BLA submission .

Each AE (preferred term) occurred as a single event in one subject, with the exception of vomiting (3 instances in 2 subjects) and extremity pain (2 instances in 1 subject). All but one AE were assessed by the investigators as unrelated to Fibryna.

A mild AE in subject # (b) (4) , 38 year old female, was assessed by the investigator as possibly related to Fibryna. This was mild skin erythema and pruritis on day 1 of the first BE. The subject was treated with diphenhydramine and hydrocortisone with resolution. This subject received two additional infusions of Fibryna, 2 days and 7 days later. She was pretreated with diphenhydramine and hydrocortisone for these infusions and did not experience any drug reactions.

Reviewer's comments: Serious AEs related to the product were not observed in Trial #2. One mild AE of transient rash occurring immediately following the infusion is considered by this reviewer to be likely related to the product. However, this event did not preclude subsequent administration of the product. The reviewer agrees with the attribution of the events as assessed by the investigator.

The reviewer concludes that the safety profile of the product is acceptable. However there are substantial limitations to interpreting the safety of the product. Of the four surgical subjects three received a single dose that was intended to achieve a plasma fibrinogen level of 100 mg/dL. Subject (b) (6) who underwent major surgery received one dose of Fibryna intraoperatively and two post-operative doses thereafter. The total dose for two subjects in the bleeding sub-group, was targeted to achieve a plasma fibrinogen level of 100 mg/dL. Congenital afibrinogenemia represents a group that is at spontaneous risk for paradoxical thrombosis of the arterial and venous type. FRT doses that target 100mg/dL and administered frequently (two to three times in a week) are known to exacerbate the thrombotic risks. To assess the safety of the dose targeted to achieve a plasma fibrinogen level of

150mg/dL, safety data for treatment in FORMA 02 that resulted in target plasma fibrinogen level >140 mg/dL was evaluated; six of the 22 bleeding events and one treatment for surgical prophylaxis (post infusion plasma fibrinogen level of 220mg/dL) were evaluated. None of seven treatments were associated with serious risks, no thrombotic events, deaths or discontinuations resulting from adverse events occurred. The limitations of the safety data is acknowledged given the absence of data in subjects with major bleeding and the limited sample size of subjects exposed to plasma fibrinogen levels of >140mg/dL. In addition, the underlying thrombotic risks in subjects with major bleeding may be different from subjects who experience minor bleeding. These limitations forms the basis for the reviewer recommendation that a safety study as a Post Marketing Requirement to evaluate the risks of thrombosis in subjects who receive doses that target plasma fibrinogen levels of 150 mg/dL should be considered at the time of marketing approval.

6.2.12.3 Deaths

No deaths were reported.

6.2.12.4 Nonfatal Serious Adverse Events

There were two serious SAEs reported, in a single subject. Subject #^{(b) (6)}, a 30 year old White, non-Hispanic male, suffered a traumatic cruciate ligament rupture and patellar fracture requiring surgical repair (two SAEs). These resolved without sequelae and were assessed by the investigator as not related to Fibryna.

6.2.12.5 Adverse Events of Special Interest (AESI)

Hypersensitivity in the form of a mild transient rash with pruritis immediately following Fibryna infusion was noted on the day of infusion. This subject received additional infusions two days later following pre-treatment with diphenhydramine without incident.

Reviewer's comment: This event of mild hypersensitivity reaction is considered related to the product. The reviewer recommends that the Warnings and Precautions section of the label should include information related to hypersensitivity reactions. Since the management of hypersensitivity reaction to Fibryna was managed as with clinical practice (corticosteroids and diphenhydramine) the clinical reviewer does not recommend including specific information regarding the management of such hypersensitivity reactions to the PI for Fibryna.

6.2.12.6 Clinical Test Results

Biomarkers of thrombogenicity

Prothrombin F1+F2

Of the 13 subjects in the study, eight subjects were noted to have elevated Prothrombin fragments F1+F2 fragments in relation to 10 treatments. Of the 10 treatments associated with F1+F2 elevations, 1 was associated with elevated pre-infusion levels only, 9 were elevated pre and post infusion, of which two

treatments were associated with higher baseline F1+F2 levels than post infusion levels.

D-dimer

Two of the 13 subjects were noted to have elevated D-dimers post infusion. A mild and transient elevation in D-dimer was noted in Subject (b) (6) two days after the infusion of Fibryna for the perioperative management of a minor surgery. Subject (b) (6) had a 2.2 fold increase in D-dimer 3 hours following the infusion. However, an additional dose was administered 3 days following the first infusion but without D-dimer elevation.

Reviewer's comment: Measurement of Prothrombin fragments F1 + F2 and D-dimer plasma levels are utilized as non-invasive screening tests to rule out DVT. Of the seven subjects with Prothrombin Fragment F1+F2 elevations only one subject (Subject (b) (6)) had corresponding elevation in D-dimer levels. These findings suggest that risk of thrombogenicity based on the two biomarkers is minimal noting that the number of subjects in the safety population is small. None of these subjects experienced a thromboembolic event during the study observation period.

Immunogenicity

Anti-fibrinogen antibodies were detected in two subjects at baseline and these persisted throughout the trial, with stable levels.

- Subject # (b) (6) , a 36 year old White non-Hispanic male had two BEs for which he received 62.5 mg/kg and 64.1 mg/kg Fibryna. Hemostatic efficacy was rated as excellent for both episodes by both the investigator and the IDMEAC. Peak fibrinogen levels for the two episodes were 109 mg/dL (IVR 1.74 mg/mL/[mg/kg]) and 95 mg/mL (IVR 1.48 mg/dL[mg/kg]). This subject also had a surgical procedure (circumcision). The maximum increase in fibrinogen postoperatively was 112 mg/mL (IVR 1.70 mg/dl[mg/kg]). Intraoperative blood loss was less than expected and hemostatic efficacy was rated as excellent by the surgeon, the hematologist and the IDMEAC.
- Subject # (b) (6) , a 25 year old White non-Hispanic female had three BE for which she received 67.8 mg/kg Fibryna. The investigator rated hemostatic efficacy as good for the first two BE and excellent for the third. The IDMEAC rated the efficacy as excellent for all three episodes. Peak fibrinogen levels were 102 mg/mL, 111 mg/mL and 92 mg/mL (IVRs 1.50, 1.64 and 1.36 mg/dL/[mg/kg]).

Reviewer's comments: In the absence of development of anti-fibrinogen antibodies, post infusion these results are interpreted in the context of limited sample size to support the safety of Fibryna with regard to immunogenicity of Fibryna and development antibodies to Fibryna. However, since anti-fibrinogen antibodies are known to occur with FRT, consideration should be made to include information for the possibility of development of anti-fibrinogen antibodies in the Warnings and Precautions section of the PI.

6.2.12.7 Dropouts and/or Discontinuations

No subjects discontinued prematurely because of an AE.

6.2.13 Study Summary and Conclusions

In this planned interim analysis, the hemostatic efficacy of Fibryna was assessed in acute BE in 10 evaluable subjects and for perioperative prophylaxis in four subjects. All acute bleeding events were minor and dosed to target a plasma fibrinogen level of 100mg/dL. Objective assessments of control following Fibryna treatment for minor bleeding events such as bruising and swelling is a challenge since the protocol did not specify measurement of the size of the bruise or swelling. To circumvent these limitations, pain and improvement of range of movement were recorded by some of the investigators. The absence of a need for additional doses of Fibryna was considered by the IDMEAC as a criterion for excellent hemostatic control. Given the type of bleeding that frequently occurs in CFD, the assessments performed for hemostatic control are considered adequate by this clinical reviewer.

Ten evaluable subjects were treated for the first bleeding event all of which were minor bleeding events with 100% success rate for hemostatic control with the lower bounds of the 90% CI at 0.78. Thus, the study met the success criterion for the primary efficacy endpoint of treatment of bleeding events with Fibryna.

The primary efficacy results were further supported by successful hemostatic control of all bleeding events in 10 evaluable subjects. 21 of 22 (95%) bleeding events met the criterion for successful hemostatic control with the lower bounds of the 90% CI at 0.80. All bleeding events were considered to be of “minor” severity.

The limitations of the data to support the efficacy conclusions include:

- The small sample size
- The absence of efficacy data for the treatment of major bleeding given that the protocol specified higher target fibrinogen levels

To address these limitations of the efficacy data with regard to treatment of major bleeding the reviewer considered the following information in support of the broader indication that included treatment of major bleeding:

- 1) Extrapolation of estimated plasma fibrinogen levels from Trial #1(FORMA 01)
- 2) The available data in the literature that supports the control of major and life-threatening bleeding at plasma fibrinogen levels of 100mg/mL following FRT
- 3) The mean plasma fibrinogen levels achieved for the treatment of minor bleeding in Trial #2 (FORMA 02)

7. INTEGRATED OVERVIEW OF EFFICACY

An integrated analysis for clinical efficacy was not performed as Trial 1 was designed to evaluate PK and PD parameters, while Trial 2 was designed to evaluate clinical endpoints of hemostatic control.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety data were categorized using MedDRA version 18.0 (Study FORMA 01) and version 18.1 (Study FORMA 02). Grading of adverse events were categorized as mild, moderate or severe.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety was assessed in both FORMA 01 and FORMA 02. Safety data were adjudicated by an Independent Data Monitoring Committee (FORMA 01) and an IDMEAC (FORMA 02).

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The total safety population included 35 subjects with congenital fibrinogen deficiency, 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 35 subjects received a mean of 101 mg/kg over 60 infusions. In FORMA 01 the mean study duration was 98.5 days, with subjects receiving a mean of 1683 mg/kg/infusion in 22 total infusions. In FORMA 02 subjects received a mean of 1408 mg/kg in a total of 25 infusions to treat BE and 445 mg/kg over a total of 13 infusions for perioperative prophylaxis.

8.2.3 Categorization of Adverse Events

All serious and non-serious AE were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) v 18.0 (FORMA 01) or v18.1 (Forma 02). A total of 30 TEAEs were reported. This includes AEs from day 1 to day 14 and SAEs from day 1 to day 45 (treatment of BE) or to day 30 (perioperative prophylaxis). There were reports of four SAEs in two subjects in the two studies requiring hospitalization and were therefore considered to be serious adverse events. Two of these serious events occurred in one subject in the FORMA 01 study and considered unrelated to Fibryna; vaginal hemorrhage and abdominal pain and trauma. The two serious events that occurred in one subject were related to a fall and therefore unrelated to Fibryna; ligament rupture and patellar fracture).

Two AE in 2 subjects were assessed by the clinical reviewer as possibly related to Fibryna. One subject in FORMA 01 developed pyrexia and thrombophlebitis following exposure to Fibryna. This subject also developed pyrexia following exposure to the

comparator product. One subject in FORMA 02 developed a mild skin reaction following Fibryna administration. This hypersensitivity reaction and pyrexia with thrombophlebitis was considered mild and related by the clinical reviewer.

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

The safety data from FORMA 01 and FORMA 02 was pooled. The treatment in FORMA 01 was fixed at 70mg/kg and administered in non-bleeding subjects with congenital afibrinogenemia whereas the dose administered was targeted to 100mg/dL in subjects with both congenital hypo and afibrinogenemia. Thus, there are limitations with regarding to comparability of dose since the dose in FORMA 01 was a flat-dose while the dose in FORMA 02 was individualized and based on the pre-treatment levels. The estimated fibrinogen plasma levels were 125mg/dL at 4 hours whereas the mean fibrinogen levels were 116 mg/dL for all 23 treatments of bleeding events. However, given the extremely rare prevalence of CFD, it will be challenging to evaluate safety of a narrow range of plasma fibrinogen levels.

8.4 Safety Results

8.4.1 Deaths

No deaths were reported for either study.

8.4.2 Nonfatal Serious Adverse Events

There were four SAE reported, two (both related, in one subject) in FORMA 01 and two (both related, in one subject) in FORMA 02. None were assessed as related to Fibryna, and this reviewer agrees.

8.4.3 Study Dropouts/Discontinuations

No subject discontinued participation prematurely.

8.4.4 Common Adverse Events

A total of 30 AE in 16 subjects were reported. The most commonly affected System Organ Class was gastrointestinal disorders (eight AE in five subjects). The most commonly reported AE was vomiting (three SAE in two subjects).

8.4.5 Clinical Test Results

Thrombogenicity

Prothrombin fragment 1 + prothrombin fragment 2 was elevated in 16 subjects after Fibryna infusion, 15 subjects in the comparator group in FORMA 01, and 13 subjects after both products. Most of these were elevated at baseline. No abnormalities in D-dimers were seen. In FORMA 02, two subjects had elevated fragment 1 + fragment 2 attributable to Fibryna (increased levels from baseline following infusion) or D-dimers on one or two occasions after receiving Fibryna. None of these laboratory findings were associated with thrombotic complications.

Immunogenicity

No subjects developed anti-fibrinogen antibodies during FORAM-02, where it was measured. Two subjects had anti-fibrinogen antibodies measured at baseline that remained stable throughout the study.

Routine Clinical Laboratory Tests

One subject in FORMA 01 had mild anemia with stable hemoglobin levels pre and 14 days post infusion. Anemia was not observed in FORMA 02 study.

8.4.6 Systemic Adverse Events

None

8.4.7 Local Reactogenicity (Hypersensitivity Reaction)

One subject developed skin erythema and pruritis after receiving Fibryna. She was premedicated without sequelae for later doses.

8.4.8 Adverse Events of Special Interest

There was a single report of local thrombophlebitis and pyrexia that is considered related to the i.v. route of administration and an expected event. There were no other reports of thromboembolic events or reports of hypersensitivity reactions.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

AE were not dose related.

8.5.2 Time Dependency for Adverse Events

AE were not related to duration of treatment.

8.5.3 Product-Demographic Interactions

There was no relationship of efficacy or safety to age, race, or geographic origin. No conclusions could be made about any relationship to ethnicity given the small subject number.

8.5.4 Product-Disease Interactions

None.

8.5.5 Product-Product Interactions

Not applicable

8.5.6 Human Carcinogenicity

There was no indication of carcinogenicity reported.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

8.5.8 Immunogenicity (Safety)

See section [8.4.5](#)

8.5.9 Person-to-Person Transmission, Shedding

Not applicable

8.6 Safety Conclusions

Of the 23 evaluable bleeding episodes in the safety population, treatment of one bleeding event did not result in any change in plasma fibrinogen levels. For the 22 subjects who were noted to have post-infusion increase in plasma fibrinogen levels and were dosed to target plasma fibrinogen levels of 100mg/dL, six subjects achieved post-infusion (1hr) plasma fibrinogen levels that were > 140 (up to a 173) mg/dL levels without any adverse events. No subject discontinued due to an AE. There was no reported anti-fibrinogen antibody development and no deaths were reported. The two adverse events considered to be related to Fibryna include one event of pyrexia with thrombophlebitis and one of hypersensitivity reaction both of which are considered as mild adverse events by the clinical reviewer. Therefore the safety profile based on the results of the pooled analysis of FORMA 01 and FORMA 02 of Fibryna supports the conclusion that the benefit risk profile favors marketing approval of Fibryna for treatment of acute bleeding episodes that includes levels targeting plasma fibrinogen levels of 150mg/dL. However, given the known risk of thrombosis from the published literature following FRT which include fibrinogen concentrates, the anticipated thrombotic risks with Fibryna dosed to target a plasma fibrinogen level of >150 mg/dL should be further evaluated in a post-marketing required study.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

There were no significant differences in efficacy or safety profiles when data were analyzed by age, sex or race, however no subject >53 years old has as yet been enrolled in a clinical trial.

9.1.1 Human Reproduction and Pregnancy Data

The safety of Fibryna during pregnancy has not been established. Clinical experience with the use of fibrinogen products to treat obstetric complications suggests there would be no harmful effects to the fetus or neonate. The label will indicate that there are no data on the use of Fibryna during pregnancy and that the product should be given to pregnant women only if clearly needed.

9.1.2 Use During Lactation

Fibryna has not been evaluated in lactating women. It is not known if the Fibryna is excreted in human milk. The draft label notes that because of this, caution should be used when administered to nursing women.

9.1.3 Pediatric Use and PREA Considerations

Fibryna is subject to PREA considerations. The applicant, in response to an Information request, submitted a request for deferral (for ages 0 to 2 years, 2 to 5 years and 6 to 12 years) in an updated section 1.9.2 (BLA 125612/0.3, July 14, 2016). Adolescents were included in the submitted clinical trials.

This efficacy and safety data in adolescent and adult study and the deferral request was discussed at PeRC on February 15, 2017. The deferred pediatric studies for the treatment of acute bleeding will be considered a pediatric PMR study if the product were to be granted marketing approval in this indication.

9.1.4 Immunocompromised Patients

This product has not been specifically evaluated in immunocompromised patients.

9.1.5 Geriatric Use

Subjects >53 years of age have not been studied.

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

None

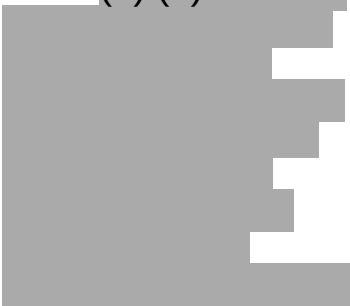
10. CONCLUSIONS

Fibryna is safe and effective for the proposed indications. Based on my review of the submitted data, this product appears safe and efficacious in adolescents and adults with afibrinogenemia or hypofibrinogenemia. An approval is recommended for the proposed indications.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 9: Summary Discussion of Benefits and Risks of Fibryna in the Eligible Population.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Afibrinogenemia and hypofibrinogenemia are rare. • Inadequate functional fibrinogen can cause a potentially fatal bleeding dyscrasia that can begin in infancy and can result in early spontaneous abortions	• Afibrinogenemia and hypofibrinogenemia are hereditary disorders that present with life-threatening bleeding
Unmet Medical Need	• There is a currently licensed fibrinogen derived from pooled human plasma	• Absent an inadequate supply of the licensed fibrinogen, RiaSTAP, there is no unmet medical need.
Clinical Benefit	• The results of one phase 2 trial and preliminary results from one phase 3 trial were submitted. All subjects had afibrinogenemia and all but one subject had a past history of bleeding episodes that had been treated with a variety of products. Efficacy was demonstrated for the treatment of acute minor bleeds. (b) (4)  No new safety concerns were identified.	• There is evidence for clinical benefit in adolescents and adults for the treatment of acute bleeding with the caveat that data to support efficacy of major bleeding is based on extrapolation of efficacy from the subjects who achieved hemostasis following a minor bleeding and the pharmacokinetic and pharmacodynamics results.
Risk	• The most substantial risks of treatment with Fibryna are thromboembolic events, hypersensitivity reactions and development of anti-fibrinogen antibodies. No antibody development during treatment was	• All the evidence indicates that Fibryna is well tolerated and safe.

	reported and there were no hypersensitivity reactions. However, these studies may have been underpowered to adequately identify these potential risks. • No SAEs were attributed to Fibryna. Four additional mild AE were possibly attributable to Fibryna: decreased hematocrit (2), mild fever, and skin reaction. • No other safety signals were apparent	
Risk Management	• The most substantial risks of treatment with Fibryna are thromboembolic events, allergic reactions and development of anti-fibrinogen antibodies. • No other safety signals were apparent.	• The safety data is limited for the treatment of acute major bleeding. Therefore the reviewer recommends a post marketing required (PMR) study to evaluate the risks of thromboembolism, immunogenicity and hypersensitivity

11.2 Risk-Benefit Summary and Assessment

Benefits: The efficacy of Fibryna has been established for on-demand treatment of BE in adults and adolescents.

Risks: No subjects developed thromboembolic events or developed anti-fibrinogen antibodies, however given the known risks of these events with FRT, the Warnings and Precautions section of the Package Insert will include this information.

11.3 Discussion of Regulatory Options

Large prospective post-marketing surveillance studies that include the patient population at large and designed to actively monitor and evaluate the risk factors for inhibitor formation, hypersensitivity reactions and thrombotic risk are important for further characterization of these risks. The submitted Pharmacovigilance Plan is sufficient to address these important potential risks. An ongoing trial (FORMA-04) will evaluate the safety and efficacy of Fibryna in pediatric subjects for the treatment of acute major or minor bleeding (b) (4) of subjects with CFD.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of this BLA. Efficacy and safety clinical data for Fibryna were found adequate to make a favorable benefit/risk determination and to support approval for the proposed indication of:

The reviewer recommends that FDA approve Fibryna for the treatment of acute bleeding episodes in adult and adolescents (children > 12 years of age) with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

11.5 Labeling Review and Recommendations

A final copy of the draft label will be included with the review memo when the revisions to the label are complete.

11.6 Recommendations on Postmarketing Actions

- Recommend post marketing study to evaluate the risks of thromboembolic events (development of anti-fibrinogen antibodies) in adults and adolescent subjects
- Recommend that FDA grant pediatric deferral request to complete pediatric study FORMA 04 study in children $\leq$ 12 years of age with a study completion date of 31st October 2021.
- Recommend that FORMA 04 is a study evaluating the efficacy of Fibryna for the treatment of acute bleeding considered a Pediatric PMR study. (b) (4) [REDACTED] is not considered a Pediatric PMR study.
- If the sponsor plans to continue studies in (b) (4) [REDACTED] an amended iPSP plan will need to be submitted to consider the FORMA 04 study as a deferred study.
- Given that the approved indication will be limited to treatment of acute bleeding, (b) (4) [REDACTED]

APPENDIX 1. ASSESSMENTS FOR ON-DEMAND TREATMENT OF ACUTE BLEEDING

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

AE = adverse event; BE = bleeding episode MCF = Maximum Clot Firmness (clot strength).

To be reviewed if period between screening and treatment is more than 3 months.

[a] If, based on daily assessment, the investigator considers an additional infusion of Octafibrin necessary (see footnote f).

[b] Within 30 minutes before infusion.

[c] Measured in local laboratories.

[d] Measured in central laboratory.

[e] Plasma retention sample for potential retesting; serum retention sample for potential viral testing.

[f] If the Octafibrin infusion administered on this day is deemed the only infusion needed for treatment of patient's

bleeding event, the post infusion assessments as detailed in the more comprehensive schedule for the Day of Last Infusion must be performed.

[g] If the actual fibrinogen plasma level is below the accepted lower limit of target fibrinogen plasma level, the patient should receive another infusion of Octafibrin. If the fibrinogen plasma level is greater than or equal to the accepted lower

limit of the target fibrinogen plasma level, Octafibrin should not be administered.

[h] Including thromboembolic events or hypersensitivity reactions.

[i] Haematology only.

Source: Study Report FORMA 02, Table 3, page 29 of 832

APPENDIX 2. ASSESSMENTS FOR PERIOPERATIVE PROPHYLAXIS

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

AE = adverse event; POP = post-operative

* ≤ 30 minutes before each infusion of *Octafibrin*.

** If considered necessary.

To be re-reviewed if period between screening and treatment is more than 3 months.

[a] ≤ 30 minutes before and after each infusion of *Octafibrin*.

[b] Measured in local laboratories.

[c] Measured in central laboratory.

[d] Plasma retain sample for potential retesting; serum retain sample for potential viral testing.

[e] If the actual fibrinogen plasma level is below the accepted lower limit of target fibrinogen plasma level, the patient should receive another infusion of *Octafibrin*. If the fibrinogen plasma level is greater than or equal to the accepted lower limit of the target fibrinogen plasma level, *Octafibrin* should not be administered.

[f] Intraoperative efficacy assessment by surgeon.

[g] Postoperative efficacy assessment by haematologist.

[h] Including thromboembolic events and hypersensitivity reactions.

Source: Study Report FORMA 02, Table 4, page 30 of 832

Do Not Change Anything Below This Line