FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
Division of Clinical Evaluation and Pharmacology/Toxicology
Pharmacology/Toxicology Branch

BLA NUMBER:	STN #125612.000
DATE RECEIVED BY CBER[1]:	June 9, 2016
DATE REVIEW COMPLETED:	April 20, 2017, amended June 6, 2017
PRODUCT[2]:	FIBRYNA (Octafibrin, Fibrinogen), a purified concentrate of fibrinogen derived from human plasma
APPLICANT:	Octapharma Pharmazeutika
PROPOSED INDICATION[3]:	Treatment of acute bleeding episodes (b) (4) in adult and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
PHARM/TOX REVIEWER:	Ying Huang
PHARM/TOX TEAM LEADER:	N/A
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PROJECT MANAGER:	Thomas J. Maruna
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OFFICE DIRECTOR:	Wilson Bryan

EXECUTIVE SUMMARY:

Octapharma has submitted an original BLA for FIBRYNA (Octafibrin, Fibrinogen), a human derived, purified concentrate of fibrinogen. The proposed indication for FIBRYNA is for treatment of acute bleeding episodes in patients with fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. In nonclinical studies, FIBRYNA behaved similarly to the marketed product Haemocomplettan® P/RiaSTAPTM with respect to pharmacodynamics and pharmacokinetic. As it is a mixture of human and plasma-derived proteins, FIBRYNA was considered reasonably safe for use in its proposed indication based on clinical experience, and on the results from single-dose toxicity studies using FIBRYNA and the nonclinical toxicity studies conducted to qualify the safety of the detergents ((b) (4)) used in the manufacturing process. The review of the pharmacological and toxicological data in support of licensure of this product is complete. There are no outstanding issues from the nonclinical discipline that would prevent approval of this BLA. However, please note that the nonclinical toxicology testing on FIBRYNA in animals has limitations in the extrapolation to

human conditions. Thus, expansion beyond the approved indication would require additional nonclinical studies to support the safety of the product.

Two non-GLP studies were conducted to evaluate the activity of FIBRYNA. Study No. 170.415.1998 ((b) (4)) evaluated the activity of FIBRYNA versus the marketed competitor product Haemocomplettan® P in a sublethal disseminated intravascular coagulation (DIC) model. This model was designed in order to induce a severe acquired hypofibrinogenaemia, mimicking thereby hypofibrinogenaemia in human patients. The study showed a significant dose–dependent increase of clot firmness at 0.75 hours and 2.25 hours after each of the Fibrinogen administration and a dose dependent shortening of thrombin time (TT) at 7 h post (b) (4) lipopolysaccharide (LPS) induction, which was similar to Haemocomplettan® P. Study No. 170.930.3495 evaluated the activity in dilutional coagulopathy model in rabbits and included the evaluations on five different batches of FIBRYNA (3/5 batches were produced by previously manufacturing process A, and 2/5 batches produced by the modified process B). The results showed similar activity measured by (b) (4) (A25) among different batches. However, no significant improvement in coagulation parameters was observed in this model.

Safety pharmacology was tested in a GLP study in which the healthy and telemetered dogs were assessed for effects on the blood pressure, heart rate, ECG, body temperature, breathing rate, hematology, coagulation parameters (activated partial thromboplastin time, prothrombin time, and fibrinogen), clinical chemistry and clinical signs. This study showed that FIBRYNA was well tolerated without test article related adverse effects. Three GLP studies for thrombogenicity were performed in rabbits each evaluating two different batches of FIBRYNA (Study No. 26063), comparability of Processes A and B with three different batches FIBRYNA (Study No. 28372), or comparability of two different nanofilters (Study No. 30767). These studies showed FIBRYNA was not thrombogenic and the results were comparable between Processes A and B products.

Three pharmacokinetic (PK) studies were conducted in rabbits and the results depicted PK parameters (AUC, C_{max}, $t_{1/2}$, and clearance) in batches produced by Process A and B. In general, the PK profiles were comparable among batches / Processes as well as to Haemocomplettan as a reference item.

Two GLP single-dose and 15-day toxicology studies were conducted in mice and rats, respectively. Although no toxicological findings, these studies were not adequately designed to capture all pertinent toxicology endpoints. Specifically, there were no clinical pathology and histopathology analyses in either of the studies. However, since the initial clinical trial was already started when the issue was identified, OBRR's decision was to defer to the clinical development for the determination of the safety of the product.

Two local tolerance studies were conducted in rabbits administered via various routes of administration. The results showed minor and transient erythema observed in the injection site following intra-arterial and intravenous administrations in mice without macroscopic or microscopic findings.

Developmental and reproductive toxicology (DART) and genotoxicity studies were not conducted.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:
There were no major nonclinical deficiencies identified in this submission, based on review of the pharmacological and toxicological data presented in STN 125612/0. There are no requests for further nonclinical testing of FIBRYNA at this time. Based on the review of the submitted toxicology and pharmacology data, this original biological application STN 125612/0 is recommended for approval for the treatment of acute bleeding episodes in patients with fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

Formulation and Chemistry:
FIBRYNA is a plasma-derived, highly purified, double virus inactivated concentrate of freeze-dried active human fibrinogen. It is supplied as a powder for reconstitution and intravenous injection. The product contains 1 gram of fibrinogen per vial. The freeze-dried powder has to be reconstituted with sterile water for injections to a solution with 20 mg fibrinogen per milliliter (b) (4) . During the production process a significant virus reduction is obtained by a combination of two dedicated inactivation/removal steps: a solvent/detergent (S/D) step for reduction of lipid enveloped viruses, and a nanofiltration step for lipid and non-lipid enveloped viruses and prions. The final reconstituted product shows (b) (4)

The potential process impurities derived from the chemicals used during manufacturing are (b) (4) . Sodium chloride, sodium citrate dehydrate, and glycine are added as (b) (4) substances. Glycine serves as a (b) (4) during the (b) (4) process. L-Arginine hydrochloride (b) (4) .

Abbreviations

A25	Clot firmness
APTT	Activated partial thromboplastin time
AUC	Area under the curve
BASO	Basophil count
CFT	Clot formation time
C_{max}	Maximum drug concentration
DIC	Disseminated intravascular coagulation
ECG	Electrocardiogram
FEIBA	Factor Eight Inhibitor Bypassing Activity
FIB	Fibrinogen
h	Hour(s)
HCT	Hematocrit
HGB	Hemoglobin
i.v.	Intravenous
LPS	(b) (4) lipopolysaccharide
MCF/A25	Maximum clot formation

MCHC	Mean corpuscular/cellular hemoglobin concentration
MCV	Mean corpuscular/cell volume
NF	Nanofiltration
NOAEL	No-Adverse-Effect Level
PLT	Platelet (thrombocyte) count
PLT	Platelet count
PT	Prothrombin time
QT_{cV}	Corrected QT interval
RBC	Red blood cell (erythrocyte) count
RET	Reticulocyte
(b) (4)	Thromboelastography
(b) (4)	
TT	Thrombin time
WBC	White blood cell (leukocyte) count

Related File(s)
IND #14777: Octapharma AG; Octafibrin (human fibrinogen) for treatment of congenital fibrinogen deficiency; ACTIVE

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INTRODUCTION

Congenital fibrinogen deficiency is an inherited coagulation disorder with considerably higher incidence in consanguineous marriages. Conditions of congenital fibrinogen deficiency include afibrinogenemia (complete absence or extremely low levels of plasma fibrinogen), hypofibrinogenemia (reduced concentration of plasma fibrinogen), and dysfibrinogenemia (presence of abnormal or dysfunctional fibrinogen molecules). Affected individuals with afibrinogenemia have a highly variable bleeding tendency that can be frequent and severe, including life-threatening bleeding and spontaneous/trauma-related bleeds.

Fibrinogen concentrate preparations are the basis for the treatment of hemorrhages in patients with congenital fibrinogen deficiency and show potential advantages over plasma and cryoprecipitate therapeutic options. FIBRYNA (Octafibrin, Fibrinogen), a plasma-derived, and purified concentrate of freeze-dried human fibrinogen, belongs to this product class.

The intended therapeutic indication is the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. FIBRYNA administration should be individualized based on the extent of bleeding, laboratory values, and the clinical condition of the patient. FIBRYNA is intended for intravenous use only. The (functional) fibrinogen plasma level should be determined in order to calculate individual dosage and the amount and frequency of administration should be based on an individual patient basis by regular measurement of plasma fibrinogen level and continuous monitoring of the clinical condition of the patient and other replacement therapies used. The normal human plasma fibrinogen level is in the range of 1.5 – 4.5 g/L. The critical plasma fibrinogen level below which hemorrhages may occur in human patients is approximately 0.5 – 1.0 g/L.

NON-CLINICAL STUDIES

Note: The proposed product, FIBRYNA, is also referred to as Octafibrin or Fibrinogen in the nonclinical study reports.

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

The following pharmacology studies were conducted to support the rationale for the administration of FIBRYNA to treat the proposed clinical indication.

In Vivo Studies

In Vivo Studies in (DIC) Animal Models

Study Number	Study Title / Publication Citation	Report Number
1	*Efficacy of Fibrinogen in the LPS induced disseminated intravascular coagulation (DIC) model in rat*	170.415.1998
2	*Efficacy study of different human fibrinogen batches in dilutional coagulopathy model*	170.930.3495

Note[4]: Study Nos. 170.415.1998 and 170.930.3495 are briefly summarized in this review memo under 'Overview of Pharmacology Studies.'

Overview of Pharmacology Studies

Overview of In Vivo Studies

Two non-GLP studies were conducted to evaluate the activity of Octafibrin (FIBRYNA). Study No. 170.415.1998 ((b) (4)) evaluated the activity of Octafibrin versus the marketed competitor product Haemocomplettan® P in a sublethal disseminated intravascular coagulation (DIC) model. This model was designed in order to induce a severe acquired hypofibrinogenaemia, mimicking thereby hypofibrinogenaemia in human patients. The study showed a significant dose–dependent increase of clot firmness at 0.75 hours and 2.25 hours after each of the fibrinogen administration and a dose dependent shortening of TT after the FIBRYNA administration at 7 h post LPS induction (2.25 h post FIBRYNA administration) were observed, which was similar to Haemocomplettan® P.

Study No. 170.930.3495 evaluated the activity in dilutional coagulopathy model in rabbits and included the evaluation of five different batches of FIBRYNA (3/5 batches were produced by previously manufacturing process A, and 2/5 batches produced by the modified process B). The results showed similar levels of clot firmness (A25), as measured by thromboelastography, among different batches. However, no significant improvement in coagulation parameters was observed in this model.

In Vivo Studies in Animal Models

Study #1

Report Number		170.415.1998
Date Report Signed		March 14, 2013
Title		*Efficacy Of Fibrinogen In The LPS Induced Disseminated Intravascular Coagulation (DIC) Model In Rat*
GLP Status		No
Testing Facility		(b) (4)
Objective(s)		To determine the activity of two batches of human fibrinogen compared to the reference Haemocomplettan
Study Animals	**Strain/Breed**	(b) (4) rats (b) (4) by (b) (4)
	Species	Rat
	Age	Adults
	Body Weight	100-250 g at arrival
	#/sex/group	80 rats/group, DIC males; 8 rats/group, healthy males
	Total #	568 males
Test Article(s)		- Two FIBRYNA (Fibrinogen) batches, Batch Nos. A019A347/U (A019) and A020A347/U (A020) - Reference item Haemocomplettan, Batch No. 06169911A manufactured by CSL Behring GmbH

Control Article(s)	- Vehicle water WFI-1, Batch No. 9510509 for the formulation of the reference item - Vehicle saline, (b) (4) Batch No. (b) (4) for preparation of the LPS formulation
Route of Administration	Intravenous (i.v.) administration at 285 min post-model induction
Description of the Disease/Injury Model and Implant Procedure	DIC model generated by injection of LPS ((b) (4)) to SD rats
Study Groups and Dose Levels	Group 0 – healthy rats, no administration Groups 1-7 – DIC rats: Group 1 – (b) (4) , 10 mL/kg Group 2 – Haemocomplettan, 100 mg/5 mL/kg Group 3 – Haemocomplettan, 200 mg/10 mL/kg Group 4 – FIBRYNA A019, 100 mg/5 mL/kg Group 5 – FIBRYNA A019, 200 mg/10 mL/kg Group 6 – FIBRYNA A020, 100 mg/5 mL/kg Group 7 – FIBRYNA A020, 200 mg/10 mL/kg
Dosing Regimen	Single i.v. administration
Randomization	Yes
Description of Masking	Not provided
Scheduled Sacrifice Time Points	5.5, 7, 24 and 72 hours post model induction

Key Evaluations and Assessments[5]*:*

- Group 0 blood sampling was performed at terminal sacrifice. For Groups 1-7, blood sampling was performed at -4 days of model induction, 5.5, 7, 24 and 72 hours post model induction; all blood samplings were terminal bleeding (n=16 DIC rats/group/time point up to 24 hours, and 32 rats/group at 72 hours).
- Body weight was assessed at animal arrival and before model induction
- Mortality and clinical observations were assessed at the same time as blood sampling
- Plasma samples were collected from the blood and analyzed for coagulation parameters, i.e., Activated partial Thromboplastin Time (APTT), Thrombin Time (TT), Prothrombin Time (PT) and Fibrinogen (FIB). APTT, TT and PT were measured by (b) (4) coagulometer, and FIB was measured by the (b) (4) method.
- Blood samples were analyzed for hematological parameters, i.e., White Blood Cell (leukocyte) count (WBC), Red Blood Cell (erythrocyte) count (RBC), and Platelet (thrombocyte) count (PLT), using a (b) (4) instrument
- Macroscopic pathology at terminal sacrifice.

Key Results:

- The observed clinical findings in all animals included ruffled hair, porphyria around the nose and eye(s), diarrhea, pale nose, ears and limbs, increased excitability, hunchback posture, ptosis, dyspnea, convulsions, paralytic hind legs, decreased activity and lying in lateral position. These symptoms were also related to the DIC induction in the animals. Thus, any putative adverse reactions related to the test article could not be discriminated in this study.

- Mortality
    - Group 1 had 5/32 animals die at the 5.5 h time point; in all other groups a higher survival rate was observed at this time point with the lowest rate in the

Haemocomplettan low-dose group (Group 2; 3/32 dead animals) and with the highest survival rate in the low-dose group of FIBRYNA batch A020A347/U (Group 6, 0/32 dead animals).
    - Between the 7- and 24-hour time points, 12/32 animals in the saline control group (Group 1) survived after 24 h. No rescue was observed in Groups 2 and 3 (Haemaocomplettan) or Groups 5 and 7 (high-dose FIBRYNA). Slightly improved survival was present in Groups 4 and 6 (low-dose FIBRYNA).
    - At the 72-hour time point, slightly improved survivals were observed in Groups 4-7, with a trend of Fibrinogen dose-dependency.

- Blood coagulation
    - APTT, PT and TT were all prolonged in the saline control group (Group 1) at least at the 5.5 h and 7 h time point as compared to the pre-values. The levels of fibrinogen of saline control group animals were strongly decreased at 5.5 h and 7 h time points, followed by a return to normal levels at 24 h and stronger elevated levels at 72 h after model induction.
    - At the 5.5 and 7 h time points, the levels of FIB were strongly elevated in the Haemocomplettan and FIBRYNA groups (Group 2 to 7) compared to the saline control group, and the FIB levels were elevated in a dose-dependent manner ranging 2.49 to 3.12 g/l at 5.5 h and 1.60 to 1.72 g/l and 7 h at the low dose, and 4.22 to 4.39 g/l at 5.5 h and at 2.35 to 3.14 g/l at 7 h. From 24 h and on the levels of FIB were similar in all groups.
    - The levels of the coagulation parameters APTT and PT were similar in all analyzed groups at all analyzed time points.
    - The TT value of the test item and reference item treated groups was strongly decreased at 5.5 h and slightly decreased at 7 h compared to the saline control group.
    - There was a significant dose–dependent increase of clot firmness at 0.75 h and 2.25 h after each of the FIBRYNA administration and a dose-dependent shortening of TT at 7 h post LPS induction, which was similar to Haemocomplettan® P.

- Hematology
    - The induction of DIC resulted in a strong decrease of platelets and leukocytes in the earliest measured time point, and in a slight reduction of erythrocytes in the latest measured time point. Administration of either the reference item or the test article did not result in significant improvement in hematology in this model.

- Macroscopic pathology
    - In general, the DIC rat showed signs of fatal systemic disorder consistent to the DIC model (e.g., porphyria, clots in tissues or free clots, dark foci, red nodules and areas in tissues as well as black content of tissues or dilated vessels that partially are black). Among others, extravasation was observed and recorded as fluid filled organs, e.g. stomach. Furthermore, signs of either degradation of blood-related products or multiple organ disorders were observed (e.g. swollen spleen and kidneys, red testes, clots in brain regions or dark foci in the liver).

- No significant improvement of the macroscopic pathology was reported following administration of the reference item and test article.

Study Report Conclusion:
In the DIC rats, the test article batches and the reference item show positive effects on the coagulation parameters FIB and TT. The survival rate was increased by 33% in the high-dose group, and by 50% in the low-dose group. No relevant differences were observed between the two analyzed batches of the FIBRYNA in this study. The reference item did not show a positive effect on the survival of the animals in the DIC model. No effect was observed on the clinical and macroscopic findings, as compared to the saline control. The FIBRYNA batches and the reference item showed positive effects on the coagulation parameters FIB and TT.

Comment:
- The survival rates in the DIC rats were improved following administration of the test article batches, however, the improvement was not in a dose-dependent manner. Thus, administration of the high dose level appears to be unnecessary.

Study #2

Report Number		170.930.3495
Date Report Signed		November 30, 2012
Title		*Efficacy Study Of Different Human Fibrinogen Batches In A Dilutional Coagulopathy Model*
GLP Status		No
Testing Facility		(b) (4)
Objective(s)		To determine the activity of different batches of human fibrinogen in the model
Study Animals	**Strain/Breed**	(b) (4) Rabbits supplied by (b) (4)
	Species	Rabbits
	Age	Adults
	Body Weight	2.2-3 kg
	#/sex/group	3 males/group
	Total #	24 males
Test Article(s)		- Five FIBRYNA (Fibrinogen) batches, Batch Nos. Process A: A019A347/U (A019), A020A347/U (A020), and A206A345/U (A206A); Process B: A205B345/U (A205B), and A205C345/U (A205C) - Reference item Haemocomplettan, Batch No. 04369911A manufactured by CSL Behring GmbH
Control Article(s)		- Vehicle water WFI-1, Batch No. 567111for formulation of the test articles - Vehicle solvent for formulation of the reference item, Batch No. 92411011A - Saline, (b) (4)
Route of Administration		Intravenous (i.v.) administration into the jugular vein via a catheter at 120 min after the first blood withdraw in Part I; or into the marginal ear vein via a catheter at 10 minutes after the end of second blood withdrawn and HEAS infusion
Description of the Disease/Injury Model and Implant Procedure		Hemodilution model was generated by withdrawing the blood and infuse with hydroxyethyl starch (HAES) in the rabbit via a catheter

Study Groups and Dose Levels	Part I: Group 2 – (b) (4) , 10 mL/kg Group 8 – Haemocomplettan, 200 mg/10 mL/kg Part II: Group 2 – (b) (4) 10 mL/kg Group 3 – FIBRYNA A019, 200 mg/10 mL/kg Group 4 – FIBRYNA A020, 200 mg/10 mL/kg Group 5 – FIBRYNA A205B, 200 mg/10 mL/kg Group 6 – FIBRYNA A205C, 200 mg/10 mL/kg Group 7 – FIBRYNA A206A, 200 mg/10 mL/kg
Dosing Regimen	Single i.v. administration
Randomization	Yes
Description of Masking	Not provided
Scheduled Sacrifice Time Points	None; in-life assessments only

Key Evaluations and Assessments[6]:

- Blood sampling for determination of APTT, PT, FIB, clotting time (CT), clot formation time (CFT), and maximum clot firmness (MCF/A25):
    - Part I: blood sampling at 0 (before the catheter implantation), 100 (after the first blood withdrawn), 135, 150, 180 and 360 minutes (i.e., 15, 30, 60 and 140 minutes post injection).
    - Part II: blood sampling at 0 (10 minutes after the catheter implantation), 10 (after the end of the blood withdrawn), 25, 40, 70 and 250 minutes (i.e., 5, 30, 60, and 240 minutes post injection).

- Clinical observations: only unexpected events (e.g., death) were recorded

Key Results:

- Part I – Both Groups 2 and 8 showed slight-moderate increase in the mean APTT at 15 - 60 minutes post injection following Haemocomplettan and vehicle administrations (negative control), while slight increase at 140 minutes post injection following Haemocomplettan administration.

- Part II – No significant changes were observed in mean APTT at any time points as compared to pre-dose in Groups 4-7. In Group 3 (FIBRYNA A019), slight-moderate increase in APTT at all the time points in study, while the increase in Group 2 ((b) (4)) was observed at 25 minutes post-injection only. A25 measured by Thromboelastography ((b) (4)) indicated that the effectiveness of different test batches was similar.

Reviewer's Comment:

- The provided data cannot conclude the presence of activity of any batches of FIBRYNA tested in this model, because there were no significant differences in APTT levels between the batches and vehicle control.

SAFETY PHARMACOLOGY STUDIES

Summary List of Safety Pharmacology Studies

The following safety pharmacology studies were conducted.

In Vivo Studies

Study Number	Study Title / Publication Citation	Report Number
3	*Safety Cardiovascular Assessment After Single Intravenous Administration Of Fibrinogen In Telemetered Conscious Dogs Including Clinical Pathology In Satellite Animals (Process A formulation)*	170.506.1993
4	*Examination Of Fibrinogen On Thrombogenic Risk In Rabbits After Intravenous Administration*	26063
5	*Examination of Different Batches of Fibrinogen for Thrombogenic Properties in Rabbits after Intravenous Administration (Processes A & B formulations)*	28372
6	*Examination of an Octafibrin Preparation for Thrombogenic Properties in Rabbits after Intravenous Administration (two different nanofilters)*	30767

Overview of Safety Pharmacology Studies

Safety pharmacology was tested in a GLP study in which conscious telemetered dogs were assessed for effects on the cardiovascular, hemodynamic and respiratory systems. This study showed that FIBRYNA was well-tolerated without drug substance related adverse effects on the cardiovascular, respiratory, hemodynamic or hematological systems. Studies were also conducted to evaluate thrombogenicity potential in rabbits. These studies showed FIBRYNA was not thrombogenic.

Overview of In Vivo Studies

A confirmatory GLP study (Study No. 170.506.1993), was conducted to examine the effects of FIBRYNA on the blood pressure, heart rate, ECG, body temperature, breathing rate, hematology (WBC, RBC, HGB, HCT, MCV, MCHC, PLT, RET), coagulation parameters (APTT, PT, FIB), clinical chemistry and clinical signs in healthy dogs.

Three GLP studies for thrombogenicity were performed in rabbits each evaluating two different batches FIBRYNA (Study No. 26063), comparability of Process A and B with three different batches FIBRYNA (Study No. 28372), or comparability of two different nanofilters (Study No. 30767).

In Vivo Studies in Healthy Animals

Study #3

Report Number	170.506.1993
Date Report Signed	February 21, 2011
Title	*Safety Cardiovascular Assessment After Single Intravenous Administration Of Fibrinogen In Telemetered Conscious Dogs Including Clinical Pathology In Satellite Animals*
GLP Status	Yes OECD Principles of GLP as revised in 1997 (ENV/MC/CHEM(98)17)

Testing Facility		(b) (4)
Objective(s)		To evaluate the effects of Fibrinogen on hemodynamic parameters, ECG, and respiratory parameters
Study Animals	**Strain/Breed**	(b) (4) supplied by (b) (4)
	Species	Dog
	Age	21-32 months
	Body Weight	8.9-13.2 kg
	#/sex/group	2 dogs/sex/group
	Total #	4 dogs/sex
Test Article(s)		FIBRYNA (Fibrinogen), Batch No. A019A347/U, dissolved in Solvent (Aqua didestillata sterilis, Batch No. 14CM26)
Control Article(s)		Vehicle (Puffer (b) (4), Batch No. (b) (4))
Route of Administration		Intravenous (i.v.)
Description of the Disease/Injury Model and Implant Procedure		N/A
Study Groups and Dose Levels		Group 1 – vehicle 12.5 mL/kg (Session I telemetered dogs) Group 2 – vehicle (Session I satellite dogs) Group 3 – test article 250 mg/12.5 mL/kg, (Session II telemetered dogs) Group 4 – test article 250 mg/12.5 mL/kg, (Session II satellite dogs) **Note**: Groups 3 and 4 reused the dogs from Groups 1 and 2; there was at least a 7-day wash-out period between the sessions for the re-administration.
Dosing Regimen		Single i.v. administration
Randomization		No
Description of Masking		Not provided
Scheduled Sacrifice Time Points		All animals were kept alive

Key Evaluations and Assessments:

In the telemetered dogs:

- Blood pressure (BP) and heart rate (HR) were recorded on the day of administration, continuously at 30 minutes before and 360 after administration, subsequently every 8 hours for additional 56 hours, followed by the final recording at 72, 84, and 96 hours post-injection. The recording time points were determined based on the applicant's kinetic data. All parameters were calculated for an approximate 30 sec average complex of the blood pressure curve recorded by telemetry using (b) (4) .

- ECG was conducted at the same sampling time intervals as BP and HR. All parameters were calculated for each 30 sec average complex of electrocardiogram recorded by telemetry. ECG assessments included arrhythmia, morphology of the T-wave, ST elevation/depression, and changes in the duration of QT interval.

- Body temperature and breath rate were taken at the same sampling time intervals as BP/HR.

- Mortality and clinical observations were conducted twice daily, and body weight once during adaptation prior to administration.

In the satellite dogs:

- Mortality, clinical observations and body weight at the same time intervals as the telemetered dogs.

- Blood samples for complete panel of clinical pathology and coagulation (APTT, PT, FIB) were collected at base line and at 30 min, 60 min, 120 min, 4 h, 6 h, 10 h, 24 h, 48 h, 72 h and 96 h post-injection.

Key Results:

- No mortality or clinical findings were reported.

- HR increase over the baseline was present during administration and returned to baseline at 60 or 75 minutes post injection in both groups with test and control articles.

- No arrhythmia or changes in T-wave morphology were observed; higher ST elevations/depressions appeared to be random without a relationship to administration of test or control articles.

- Changes in the ECG parameters (RR duration, QT duration,) appeared to be related to HR changes. The average QT_{cV} (corrected QT duration) could not completely correct the QT values (-24 to +15% compared to base line), which occurred most in males of both groups with test and control articles.

- 15 minutes post-injection in both test and control articles groups, body temperature slightly increased (1-3%) and respiratory rate slightly increased (13-16%).

- Coagulation analysis showed the FIB levels were increased markedly following test article administration. In males, 99% increase over the baseline occurred at 60 minutes to 4 h post-injection, followed by a decrease down to 39% at 96 h. In females, the maximum concentration (122%) occurred at 30 minutes to 10 h post-injection followed by a slow decrease to 31% at 96 h.

- Hematologic analysis indicated moderate increases in relative basophil count (BASO) in test article administered males (2-6 fold over the baseline at all time points) and females (up to 4 fold over the base line at 30 – 48 h post injection). All values were within the physiological range of the species. No other hematologic findings or serum chemistry findings were reported.

Study Report Conclusion:

- The i.v. administration of the test article at 250 mg/kg was estimated at being around the NOAEL (No-Adverse-Effect Level).

Study #4

Report Number	26063

Date Report Signed		June 10, 2011
Title		*Examination of Fibrinogen on Thrombogenic Risk in Rabbits after intravenous Administration*
GLP Status		Yes OECD Principles of GLP as revised in 1997 (ENV/MC/CHEM(98)17, & ENV/JM/MONO (2002)9)
Testing Facility		(b) (4)
Objective(s)		To evaluate the test article on thrombogenic risk in rabbits
Study Animals	**Strain/Breed**	(b) (4)
	Species	Rabbit
	Age	3.5-5 months
	Body Weight	1.8-2.1 kg
	#/sex/group	5 males/group
	Total #	20 males
Test Article(s)		FIBRYNA (Fibrinogen), Batch Nos. A019A347/U (A019), and A020A347/U (A020)
Control Article(s)		Positive control was Factor Eight Inhibitor Bypassing Activity (FEIBA) Batch No. VNF 2J038, and negative control was vehicle (formulation buffer) Batch No. OPS0721V1
Route of Administration		Intravenous (i.v.)
Description of the Disease/Injury Model and Implant Procedure		N/A
Study Groups and Dose Levels		Group 1 – vehicle 20 mL/kg Group 2 – FIBRYNA A020, 400 mg/20 mL/kg Group 3 – FIBRYNA A019, 400 mg/20 mL/kg Group 4 – FEIBA, 100 U/2 mL/kg
Dosing Regimen		Single i.v. administration
Randomization		No
Description of Masking		Not provided
Scheduled Sacrifice Time Points		Animal sacrificed 10 minutes post injection, but no further examination was carried out

The experiment was conducted based on the article by (b) (4) .

Key Evaluations and Assessments:
Within 25 seconds after completion of the injection, the previously exposed vena jugularis was gently ligated (on a length of 1 - 2 cm). This ligated vein segment remained *in situ* for 10 minutes. The segment was then removed from the animal, its contents were emptied into a Petri dish containing a sodium citrate solution and the contents of the dish were examined.

Key Results and Conclusion:
Under the test condition, the test articles did not show any thrombogenic effect. The mean score of the positive control group with FEIBA was 4.0 with a single thrombus forming a cast of the isolated segment.

Study #5

Report Number	28372
Date Report Signed	July 5, 2012
Title	*Examination of Different Batches of Fibrinogen for Thrombogenic Properties in Rabbits after intravenous Administration*

GLP Status		Yes OECD Principles of GLP as revised in 1997 (ENV/MC/CHEM(98)17, & ENV/JM/MONO (2002)9)
Testing Facility		(b) (4)
Objective(s)		To compare three batches of the test article on thrombogenic risk in rabbits
Study Animals	**Strain/Breed**	(b) (4)
	Species	Rabbit
	Age	3 months
	Body Weight	2.4-2.5 kg
	#/sex/group	3 males/group
	Total #	9 males
Test Article(s)		FIBRYNA (Fibrinogen), Batch Nos. A205B345/U (A205B), A205C345/U (A205C), and A206A345/U (A206A)
Control Article(s)		Positive control was Factor Eight Inhibitor Bypassing Activity (FEIBA) Batch No. VNF 2J038, and negative control was vehicle (formulation buffer) Batch No. OPS0721V1
Route of Administration		Intravenous (i.v.)
Description of the Disease/Injury Model and Implant Procedure		N/A
Study Groups and Dose Levels		Group 1 – FIBRYNA A205B, 400 mg/20 mL/kg Group 2 – FIBRYNA A205C, 400 mg/20 mL/kg Group 3 – FIBRYNA A206A, 400 mg/20 mL/kg
Dosing Regimen		Single i.v. administration
Randomization		No
Description of Masking		Not provided
Scheduled Sacrifice Time Points		Animal sacrificed 10 minutes post injection, but no further examination was carried out

The experiment was conducted based on the article by (b) (4) .

Key Evaluations and Assessments:
Within 25 seconds after completion of the injection, the previously exposed vena jugularis was gently ligated (on a length of 1 - 2 cm). This ligated vein segment remained *in situ* for 10 minutes. The segment was then removed from the animal, its contents were emptied into a Petri dish containing a sodium citrate solution and the contents of the dish were examined.

Key Results and Conclusion:
Under the test condition, none of the three batches of test article showed any thrombogenic effect.

Study #6

Report Number	30767
Date Report Signed	February 20, 2014
Title	*Examination of an Octafibrin Preparation for Thrombogenic Properties in Rabbits after intravenous Administration*
GLP Status	Yes OECD Principles of GLP as revised in 1997 (ENV/MC/CHEM(98)17, & ENV/JM/MONO (2002)9)
Testing Facility	(b) (4)

Objective(s)		To evaluate the test article on thrombogenic risk in rabbits
Study Animals	**Strain/Breed**	(b) (4)
	Species	Rabbit
	Age	3 months
	Body Weight	2.3-2.5 kg
	#/sex/group	5 males/group
	Total #	15 males
Test Article(s)		FIBRYNA (Octafibrin), Batch No. C344A347/U
Control Article(s)		Positive control was Factor Eight Inhibitor Bypassing Activity (FEIBA) Batch No. VNF 2N047A, and negative control was saline
Route of Administration		Intravenous (i.v.)
Description of the Disease/Injury Model and Implant Procedure		N/A
Study Groups and Dose Levels		Group 1 – FIBRYNA 400 mg/20 mL/kg Group 2 – FEIBA 30 U/20 mL/kg Group 3 – Saline 20 mL/kg
Dosing Regimen		Single i.v. administration
Randomization		No
Description of Masking		Not provided
Scheduled Sacrifice Time Points		Animal sacrificed 10 minutes post injection, but no further examination was carried out

The experiment was conducted based on the article by (b) (4) .

Key Evaluations and Assessments:
Within 25 seconds after completion of the injection, the previously exposed vena jugularis was gently ligated (on a length of 1 - 2 cm). This ligated vein segment remained *in situ* for 10 minutes. The segment was then removed from the animal, its contents were emptied into a Petri dish containing a sodium citrate solution and the contents of the dish were examined.

Key Results and Conclusion:
Under the test condition, the test articles did not show any thrombogenic effect. The mean score of the positive control group with FEIBA was 4.0 with a single thrombus forming a cast of the isolated segment.

PHARMACOKINETIC STUDIES

Summary List of Pharmacokinetics Studies

The following pharmacokinetic studies were conducted.

In Vivo Studies

Study Number	Study Title / Publication Citation	Report Number
7	*Pharmacokinetics study of Fibrinogen (fibrinogen human freeze dried) in two different batches and haemocomplettan after single intravenous administration in female* (b) (4) *rabbits (Process A)*	170.214.1992

Study Number	Study Title / Publication Citation	Report Number
8	*Pharmacokinetics of human Fibrinogen after a single administration in female* (b) (4) *rabbits (Process A & B)*	170.222.3491
9	*Pharmacokinetic study in rabbits following single intravenous administration of FIBRYNA preparations (two different nanofilters)*	30765

Study #7

This study determined the PK profile of two batches of FIBRYNA manufactured with Process A. 24 female (b) (4) rabbits were divided into four groups (n = 6 rabbits/group i.v. administered with vehicle, Haemocomplettan 100 mg/5 mL/kg, FIBRYNA A020 and FIBRYNA A019 at 100 mg/5 mL/kg). Blood samples were collected at baseline, and 1, 2, 4, 6, 10, 24, 48, 72, 96, 120, 180, and 240 h after i.v. injection. Plasma levels of FIB were analyzed for the determination of the PK profile.

The results showed mean maximum plasma concentrations were similar among the two batches of FIBRYNA (AUC_{last} = 73.5 - 77.3 h*mg/ml) as well as the reference item. The relative bioavailability calculated by the ratio to the reference item was 101% for FIBRYNA A020 and 97% for FIBRYNA A019. The mean terminal elimination half-life $t_{1/2}$ was 44.6 h for A020 and the reference item, and 44.1 h for A019.

Study #8

This study compared the PK profiles of FIBRYNA manufactured with Process A and B. 21 female (b) (4) rabbits were divided into 7 groups (n = 3 rabbits/group, i.v. administration, three batches of the Process A product and two batches of the Process B product, one batch of the reference item, and one vehicle control). Blood samples were collected at base line, and 1, 4, 10, 24, 48, 96, and 120 hours after i.v. injection. Plasma levels of FIB were analyzed for the determination of the PK profile. The PK profiles were similar among 2/3 batches of the Process A, 1/2 batches of the Process B products, AUC_{last} = 100 h*mg/ml, and the reference item. The PK profiles of the remaining batches (AUC_{last} = 83 or 119 h*mg/ml) were slightly off the reference item. The mean terminal elimination half-life $t_{1/2}$ was 40 h for all the batches.

Study #9

This study compared the PK profiles of two FIBRYNA batches produced before and after a filter replacement for nanofiltration (NF). FIBRYNA Batch Nos. C344A347/U (new NF) and C227A347/U (old NF), the reference item Haemocomplettan® P and the vehicle (Formulation buffer) as negative control item were administered i.v. to (b) (4) rabbits at 100 mg/kg. The results showed similar PK profiles among these three batches.

TOXICOLOGY STUDIES

Summary List of Toxicology Studies

The following toxicology studies were conducted to evaluate the safety of FIBRYNA following administration in various animal species.

Toxicology Studies:

Study Number	Study Title / Publication Citation	Report Number
10	*Single Dose Intravenous Toxicity Study with Fibrinogen in Male and Female* (b) (4) *Mice (process A)*	170.110.1990
11	*Single Dose Intravenous Toxicity Study with Fibrinogen in Male and Female* (b) (4) *Rats (Process A)*	170.110.1991

Developmental and Reproductive Toxicology Studies:

Studies were not conducted to evaluate this safety endpoint because this evaluation has historically not been required for this product class.

Genotoxicity Studies:

Studies were not conducted to evaluate this safety endpoint because this evaluation is not required for this product class.

Other Safety/Toxicology Studies

Study Number	Study Title / Publication Citation	Report Number
12	*Local Tolerance Test in Rabbits after a Single Intravenous, Intra-arterial and Paravenous Administration of Fibrinogen in Two Different Batches versus Control (Process A)*	170.143.1989
13	*Study on Local Tolerance after Single Intravenous, Intra-arterial and Paravenous Administration in Rabbits with an Octafibrin Preparation (two different nanofilters)*	30766

Note: Report Nos. 5123/88, 5124/88, 5125/88, 5126/88, 5127/88, 5128/88, 5568/1/89, 5569/1/89, 6086/90, 6087/90, 6088/90, 6089/90, 6091/90, 6343/90, 6344/90, 6345/90, 7724/92, 7725/92, Dec/24/1986, Dec/30/1986, and Nov/5/1986 are not listed or summarized in this review memo because these reports evaluated the safety of a (b) (4) , which have been licensed by the Federal German Health Office since 1990, and all these study reports were with the license. The BLA applicant has not conducted any preclinical studies with this combination.

Toxicology Studies

Study #10

Report Number	170.110.1990
Date Report Signed	December 17, 2010
Title	*Single Dose Intravenous Toxicity Study With Fibrinogen In Male And Female* (b) (4) *Mice*

GLP Status		Yes OECD Principle of GLP as revised in 1997 (ENV/MC/CHEM(98)17)
Testing Facility		(b) (4)
Objective(s)		To determine the acute toxicity of Fibrinogen in male and female (b) (4) mice after a single intravenous administration of three doses
Study Animals	**Strain/Breed**	(b) (4)
	Species	Mice
	Age	8 weeks
	Body Weight	Males 33.2-37.6 g, Females 27.9-32.5
	#/sex/group	5 mice
	Total #	20 mice/sex
Test Article(s)		FIBRYNA (Fibrinogen) Batch No. A019A347/U
Control Article(s)		Vehicle Batch No. 10PRAR0825
Route of Administration		Intravenous (i.v.)
Description of the Disease/Injury Model and Implant Procedure		N/A
Study Groups and Dose Levels		Group 1 – vehicle, 50 mL/kg Group 2 – FIBRYNA 200 mg/10 mL/kg Group 3 – FIBRYNA 500 mg/25 mL/kg Group 4 – FIBRYNA 1,000 mg/50 mL/kg
Dosing Regimen		Single i.v. administration
Randomization		Yes
Description of Masking		Not provided
Scheduled Sacrifice Time Points		Terminal sacrifice on day 15 post-injection

Key Results:

- No mortality, clinical findings or body weight changes were reported.
- No abnormal findings in macroscopic pathology were reported.

Reviewer Comment:

- Clinical pathology and histopathology were not conducted for this study. The utility of this study to determine the safety of FIBRYNA is questionable. However, data from the completed clinical studies can be used to determine the safety of FIBRYNA.

Study #11

Report Number		170.110.1991
Date Report Signed		December 20, 2010
Title		*Single Dose Intravenous Toxicity Study With Fibrinogen In Male And Female* (b) (4) *Rats*
GLP Status		Yes OECD Principle of GLP as revised in 1997 (ENV/MC/CHEM(98)17)
Testing Facility		(b) (4)
Objective(s)		To determine the acute toxicity of Fibrinogen in rats after a single intravenous administration of three doses
Study Animals	**Strain/Breed**	(b) (4)
	Species	Rats
	Age	8 weeks
	Body Weight	Males 239-270 g, Females 194-221 g
	#/sex/group	5 rats
	Total #	20 rats/sex

Test Article(s)	FIBRYNA (Fibrinogen) Batch No. A020A347/U
Control Article(s)	Vehicle Batch No. 10PRAR0825
Route of Administration	Intravenous (i.v.)
Description of the Disease/Injury Model and Implant Procedure	N/A
Study Groups and Dose Levels	Group 1 – vehicle, 25 mL/kg Group 2 – FIBRYNA 200 mg/10 mL/kg Group 3 – FIBRYNA 300 mg/15 mL/kg Group 4 – FIBRYNA 500 mg/25 mL/kg
Dosing Regimen	Single i.v. administration
Randomization	Yes
Description of Masking	Not provided
Scheduled Sacrifice Time Points	Terminal sacrifice on day 15 post injection

Key Results:

- No mortality or clinical findings changes were reported.
- A slight body weight loss was observed in two males administered with 500 mg/kg Fibrinogen between day 0 and 2 (approx. 1.2 and 0.7 % loss). Given the small number of animals and small decrease in weight loss, this finding may be individual variation.
- No abnormal findings in macroscopic pathology were reported.

Reviewer Comment:

- Clinical pathology and histopathology were not conducted for this study. The utility of this study to determine the safety of FIBRYNA is questionable. However, data from the completed clinical studies can be used to determine the safety of FIBRYNA.

Study #13

Report Number		170.143.1989
Date Report Signed		November 25, 2010
Title		*Local Tolerance Test In Rabbits After A Single Intravenous, Intraarterial And Paravenous Administration Of Fibrinogen (Fibrinogen Human Freeze Dried) In Two Different Batches Versus Control*
GLP Status		No
Testing Facility		(b) (4)
Objective(s)		To determine the local tolerance
Study Animals	**Strain/Breed**	(b) (4)
	Species	Rabbits
	Age	Not provided
	Body Weight	2.1 – 2.4 kg
	#/sex/group	2 rabbits
	Total #	4 rabbits/sex
Test Article(s)		FIBRYNA (Fibrinogen) Batch Nos. A019A347/U (A019) and A020A347/U (A020)
Control Article(s)		Vehicle Batch No. 10PRAR0825; solvent (aqua bidestillata sterilis)
Route of Administration		Intravenous (i.v., lateral vein of the inner ear), intraarterial (i.a., medial artery of the ear), or paravenous (p.v., subcutaneous area of lateral vein of the ear)
Description of the Disease/Injury Model and Implant Procedure		N/A

Study Groups and Dose Levels	Group 1 – FIBRYNA A020, left ear, i.v. 100 mg/5 mL/rabbit; vehicle, right ear, i.v. 5 mL/rabbit; FIBRYNA A020, left ear, i.a. 100 mg/5 mL/rabbit; vehicle, right ear, i.a. 5 mL/rabbit; FIBRYNA A020, left ear, p.v. 2 mg/0.1 mL/rabbit; vehicle right ear, p.v. 0.1 mL/rabbit Group 2 – FIBRYNA A019, left ear, i.v. 100 mg/5 mL/rabbit; solvent, right ear, i.v. 5 mL/rabbit; FIBRYNA A019, left ear, i.a. 100 mg/5 mL/rabbit; solvent, right ear, i.a. 5 mL/rabbit; FIBRYNA A019, left ear, p.v. 2 mg/0.1 mL/rabbit; solvent right ear, p.v. 0.1 mL/rabbit
Dosing Regimen	Single administration
Randomization	No
Description of Masking	Not provided
Scheduled Sacrifice Time Points	Terminal sacrifice on day 4 post injection

Key Results:

- Erythema was observed in female rabbits i.a. injected with FIBRYNA A020, and in males i.a. injected with FIBRYNA A019. Erythema was also observed in females i.v. injected with FIBRYNA A020. These findings were minor and short duration. Erythema was present at 3-24 h post p.v. injection to males with FIBRYNA A019.

- Edema, pain reaction or other clinical signs were not observed in any of the study animals.

- No abnormal macroscopic or microscopic findings of the injection sites were reported

The study report concluded that Fibrinogen was well-tolerated to local injection.

Study #14

Report Number		30766
Date Report Signed		May 12, 2014
Title		*Study on Local Tolerance after Single Intravenous, Intra-Arterial and Paravenous Administration in Rabbits with an Octafibrin Preparation*
GLP Status		Yes OECD Principle of GLP Document Nos. 1, 8, and 13 ENV/MC/CHEM(98)17, ENV/JM/MONO (99) 24 and ENV/JM/MONO (2002) 9, respectively
Testing Facility		(b) (4)
Objective(s)		To obtain information on the local tolerance of an FIBRYNA (Octafibrin) Preparation in rabbits
Study Animals	**Strain/Breed**	(b) (4)
	Species	Rabbits
	Age	Males 2.5-3.5 months; females 3.5-4.5 months
	Body Weight	Males 3.4-3.8 kg, Females 3.4-4.0 kg
	#/sex/group	2 rabbits
	Total #	6 rabbits/sex
Test Article(s)		FIBRYNA (Octafibrin), Batch No. C344A347/U
Control Article(s)		None

Route of Administration	Intravenous (i.v., 60-minute infusion into the marginal vein of the ear), intraarterial (i.a., 10-minute infusion into the central artery of the ear), or paravenous (p.v., paravenous subcutaneous beside the marginal vein of the ear)
Description of the Disease/Injury Model and Implant Procedure	N/A
Study Groups and Dose Levels	Group 1 – 100 mg/5 mL/rabbit, i.v. Group 2 – 100 mg/5 mL/rabbit, i.a. Group 3 – 2 mg/0.1 mL/rabbit, p.v.
Dosing Regimen	Single administration
Randomization	Yes
Description of Masking	Not provided
Scheduled Sacrifice Time Points	Terminal sacrifice on day 4 post injection

Key Results:

- No clinical signs of systemic toxicity or mortality were reported.
- Macroscopic findings included slight eschar formation in 1/2 male and slight redness in 1/2 female following i.a. administration.
- Microscopic findings included mild infiltration of macrophages and lymphocytes of the injection site in 1/2 males following i.a. administration.

The study report concluded that FIBRYNA was well-tolerated to local injection.

APPLICANT'S PROPOSED LABEL

Section 8 ('Use in Specific Populations') was revised to comply with 21 CFR 201.56(d)(1), 201.57(c)(9), and 201.57(c)(14)[1].

Section 13 ('Nonclinical Toxicology') was removed since genotoxicity and carcinogenicity studies were not conducted with FIBRYNA.

CONCLUSION OF NON-CLINICAL STUDIES

Review of the nonclinical studies did not identify any safety concerns that could not be adequately addressed in labeling (see above recommendations regarding the label). The nonclinical data support approval of the license application.

KEY WORDS/TERMS

FIBRYNA, Octafibrin, Fibrinogen, fibrinogen derived from human plasma, acute bleeding episodes, congenital fibrinogen deficiency, coagulation, rabbits, dogs.

[1] Pregnancy and Lactation Rule (PLLR), at: http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/actsrulesregulations/ucm445102.htm.

[1] If the application is a rolling submission, cite the dates that the P/T, CMC, and clinical modules were received.

[2] Cite the proposed product name and description stated in bold at the beginning of the draft Package Insert (PI).

[3] Cite the proposed clinical indication stated under 'Indications and Usage' in the draft PI.

[4] Briefly summarize the submitted relevant pharmacology/proof-of-concept (POC) studies conducted by the study sponsor or applicant and/or the studies cited from the scientific literature. The selected studies should help inform the text in Section 12.1 of the draft PI ['Mechanism of Action'].

[5] Provide a description of the in-life and post-mortem assessments.
[6] Provide a description of the in-life and post-mortem assessments.