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Summary Basis for Regulatory Action

Note: The SBRA was modified from the original to correct the dating specifications for post-marketing commitments and other minor errors.

Date	February 25, 2009
From	Laura Wood, Committee Chair
Subject	Summary Basis for Regulatory Action
BLA # Supplement#	STN 125317/0
Applicant	CSL Behring GmbH
Date of Submission	July 18, 2008
PDUFA Goal Date	January 17, 2009
Proprietary Name / Established (USAN) names	RiaSTAP™/Fibrinogen Concentrate (Human)
Dosage forms	Lyophilized, 1 g dose (900-1300 mg/vial)
Proposed Indication(s)	Treatment of acute bleeding in patients with congenital fibrinogen deficiency, afibrinogenemia and hypofibrinogenemia
Recommended Action:	Approval
Signatory Authority(ies) Action	**Basil Golding**_____ *Offices Signatory Authority:* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum*

Material Reviewed/ Consulted SBRA	**List of specific documentation used in compiling**
Clinical Review	Nisha Jain
Statistical Review	Boris Zaslavsky
Pharmacology/ Toxicology Review	La'Nissa Brown
CMC Review/Facilities	Laura Wood, Roman Drews, Ze Peng/ Rebecca Olin
EIR	N/A
Biomonitoring Review	Christine Drabick
Advisory Committee Transcript	
Labeling	Loan Nguyen
Clinical Pharmacology	Iftekhar Mahmood

Other Signatory authorities:

Jay Eltermann_____

1. Introduction

CSL Behring GmbH has submitted an original biological licensing application for Fibrinogen Concentrate (Human) for the treatment of acute bleeding episodes in congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. The product will be available in lyophilized form and will be administered intravenously.

Fibrinogen (Factor I) is a soluble plasma glycoprotein with a molecular weight of approximately 340 kDa. The native molecule is a homo-dimer. Both subunits contain three different polypeptide chains (Aα, Bβ, and γ γ). During the clotting process, thrombin cleaves the amino terminal ends of the Aα and Bβ chains. The resulting fibrin monomers are then capable of polymerization by end-to-end and side-to-side aggregation. Factor XIIIa effects cross-linking of the polymers, making the clot more elastic and resistant to fibrinolysis. The cross-linked fibrin gives tensile strength to the primary hemostatic platelet plug.

2. Background

Fibrinogen for intravenous use was marketed in the United States by several companies in the twentieth century. It was used to treat not only congenital fibrinogen deficiency, but also to treat obstetric (post-partum) bleeding. The FDA revoked all licenses for fibrinogen concentrates in 1977 because of the risk for hepatitis infection and a suspected lack of effectiveness in obstetric use. Several fibrin sealants are currently licensed in the U.S., but no fibrinogen for intravenous use is currently licensed. When licensed, RiaSTAP™ will have orphan drug status in the U.S. The BLA was submitted under the Accelerated Approval procedure.

CSL Behring GmbH and its predecessors have manufactured human fibrinogen concentrate since 1956. Fibrinogen concentrate for therapeutic use in humans with congenital or acquired fibrinogen deficiency was previously known under the trade names “Human Fibrinogen Konzentrat” and “Human Fibrinogen Behringwerke Konzentrat”. The product was renamed Haemocomplettan® P 1g/2/ in 1985, coinciding with significant improvements in purity and safety, with the implementation of a heat treatment step. The basic manufacturing process has remained unchanged from this time, with the exception of increases in production scale or necessary updates to GMP and pharmaceutical industry technology standards. The manufacturing process of RiaSTAP™ is identical to the current manufacturing process of Haemocomplettan® P, except that the cryoprecipitate and the albumin solution used as stabilizer are produced by U.S. licensed facilities. Haemocomplettan® P is currently marketed in a 9 European countries and elsewhere.

3. Chemistry, Manufacturing and Controls (CMC) and Facilities

CMC

Manufacture:

The manufacturing process begins at the CSL Behring (b) (4) facility in (b) (4) . U.S. licensed source plasma is the starting material for isolation of cryoprecipitate, which is shipped frozen to the CSL Behring GmbH facility in Marburg, Germany. The cryoprecipitate is (b) (4) to inhibit the action of (b) (4) . Contaminating proteins such as the (b) (4) factors are largely removed by adsorption to $Al(OH)_3$. A glycine precipitation then eliminates some other proteins. A second $Al(OH)_3$ adsorption ensures almost complete removal of the (b) (4) . The (b) (4) containing the fibrinogen is then stabilized by the addition of (b) (4) , followed by heat treatment at 60ºC (b) (4) for 20 (b) (4)) h to inactivate potentially present viruses. After dilution with buffer, the solution undergoes two more glycine precipitations, and the final precipitate may be stored (b) (4) , the precipitate is dissolved, (b) (4) and dialyzed to remove residual (b) (4) followed by filtration and (b) (4) . L-arginine monohydrochloride and human albumin are added, and the fibrinogen bulk is sterile-filtered, filled, lyophilized, and capped.

Control of starting materials:

All plasma used in the manufacture of RiaSTAP™ is tested using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV. Additionally, the plasma is tested with FDA-licensed Nucleic Acid Testing (NAT) for HCV and HIV-1 and found to be non-reactive. For HBV, an investigational NAT procedure is used; however, the significance of a negative result has not been established. The plasma has also been tested by NAT for HAV and B19V. Only plasma units that passed virus screening are used for production, and the limit for B19V in the fractionation pool is set not to exceed 10^4 IU of B19V DNA per mL.

(b) (4) is added early in the manufacturing process, but is removed in subsequent purification steps. (b) (4) is of concern because of recent contaminants in (b) (4) sold by (b) (4) , causing adverse events in patients. However, the (b) (4) used by CSL Behring is supplied by (b) (4)) and produced by (b) (4) and at (b) (4) . There are no links between their supply chains of (b) (4) and those of (b) (4) . Furthermore, CSL Behring's quality control department has been performing additional tests on (b) (4) that are recommended by the FDA since 2004 (b) (4) . The analyses clearly confirm that none of the (b) (4) batches received from (b) (4) have contained the dangerous contaminant.

Viral reduction and inactivation steps:

The manufacturing process has been demonstrated to reduce the risk of virus transmission in an additive manner: heat treatment, cryoprecipitation, and other adsorption/precipitation steps have been validated in a series of *in vitro* experiments for their capacity to inactivate a wide range of viruses of diverse physicochemical characteristics, including: Human Immunodeficiency Virus, Hepatitis A Virus, B19 Virus, West Nile Virus, Herpes Simplex Virus type 1; and the following model viruses: Bovine Viral Diarrhea Virus as a model for Hepatitis C Virus, and Canine Parvovirus as a model for Parvovirus B19.

CBER normally expects that two dedicated viral clearance steps will be included in the manufacturing process for a biologic product. However, in this case the product has been marketed in other countries for many years without significant viral safety concerns. Therefore, the review committee has decided that insisting on the addition of another viral inactivation step to the manufacturing process is unnecessary. The following table summarizes the viral reductions of the manufacturing steps.

Cumulative (Log_{10}) Virus Inactivation/Reduction in RiaSTAP

Manufacturing Step	**Virus Reduction Factor (log_{10})**							
	Enveloped viruses					**Non-enveloped viruses**		
	HIV	**BVDV**	**WNV**	**HSV-1**	**PRV**	**HAV**	**CPV**	**B19V***
Cryoprecipitation	n.d.	n.d.	n.d.		1.6†	2.4	2.8	n.d.
$Al(OH)_3$ adsorption/ glycine precipitation/ $Al(OH)_3$ adsorption	(2.8)‡	(1.5)‡	n.d.	(0.9)‡				n.d.
Heat Treatment	≥ 5.7	≥ 9.1	≥ 8.3	≥ 8.1		≥ 4.3	1.6	≥ 4.5*
Glycine precipitation (two subsequent steps)	3.9	2.1	n.d.	1.0		(1.0)‡	(1.6)‡	n.d.
Cumulative virus reduction (log_{10})	**≥ 9.6**	**≥ 11.2**	**≥ 8.3**	**≥ 9.1**	**1.6**	**≥ 6.7**	**4.4**	**≥ 4.5**

BVDV, bovine viral diarrhea virus, model for HCV

WNV, West Nile virus

HSV-1, herpes simplex virus type 1

CPV, canine parvovirus, model for B19V

*B19V, human parvovirus B19, the virus elimination studies for parvovirus B19 employed a novel experimental infectivity assay utilizing clone of cell line UT7 that contains erythropoietic progeny cells. Virus titer was determined using an immunofluorescence-based detection method.

† PRV – as HSV-1 a herpes virus – is reduced by cryoprecipitation by 1.6 log_{10}

‡ Not included in the calculation of the cumulative virus reduction factor.

n.d., not done

Stability Studies

Stability studies are ongoing. The results currently support a 30 month shelf-life at 2°C to 25°C.

Analytical Methods

Analytical methods have been validated or are covered by European or US Pharmacopoeias.

CBER Lot Testing and Review

Conformance lot testing has been performed at CBER for the following: sterility, LAL, moisture, solubility, appearance, and pH.

The product will be under lot release at CBER for protocol review only.

Conclusions

The CMC reviewers (Laura Wood, Roman Drews, and Ze Peng) find that CSL Behring GmbH has provided sufficient data and information on the chemistry, manufacture and controls to support licensure of RiaSTAP.

FACILITIES AND EQUIPMENT

Site Description

Drug substance and final bulk solution will be manufactured at CSL Behring GmbH located in Marburg Germany (License #1765). Pre-treatment of equipment is conducted at the Main Work site. Manufacture of the (b) (4) (b) (4) are conducted at the (b) (4) complex in Marburg. (b) (4) will be manufactured at CSL Behring (b) (4) located in (b) (4) (b) (4) US (License #(b) (4) Human albumin excipient will be manufactured at CSL Behring (b) (4) in (b) (4) (License #(b) (4)

The facilities used for the manufacture and testing of HFCP are included in the table below:

Building	Manufacturing Operation	Relevant Floor	Location
(b) (4)			

Process Validation

Full-scale process validation studies were conducted by manufacturing (b) (full scale fibrinogen lots which were used in three consecutive HFCP lots and three consecutive Fibrinogen Active Substance lots. These lots were manufactured under routine conditions at full-scale to validate the effect of individual processing steps and holding times on particular process quality attributes (PQAs). These studies used target values for all process steps; however holding and filling times were validated at full-scale under worst-case conditions.

Three consecutive batches of lyophilized product were manufactured in support of the lyophilization process using lyophilizers (b) (4) .

Full-scale investigation studies were conducted in parallel with routine production to evaluate the bioburden and endotoxin levels (b) (4) . These studies were also conducted to identify the major potential impurities ((b) (4) (b) (4) at the main purification steps including the lyophilized product.

Media Fills

Aseptic processing conditions were validated by simulation using sterile nutrient medium and were performed under the same production conditions as the drug product.

Drug Substance: Three consecutive runs were conducted to validate the aseptic process in the (b) (4) .

Drug Product: (b) (4) media fill runs were conducted to validate the aseptic processing on filling and stoppering machine (b) (4) and lyophilizers (b) (4) (b) (4) located in Building (b) (4) Routine and non-routine interventions were included in the studies and were identified in the final report.

Container Closure

Drug Substance: The drug substance of HFCP, final bulk solution, is obtained after (b) (4) final adjustment and sterilizing filtration of the bulk solution. The final bulk solution is stored in (b) (4) and can be stored up to (b) (4) at (b) (4) (b) (4) . Holding/storage times and container closure integrity of the final bulk vessels have been validated using (b) (4) to verify the tanks ability to maintain sterility for up to (b) (4) .

Drug Product: Single-dose 100-mL infusion vials made of (b) (4) glass along with gray (b) (4) rubber stoppers and an (b) (4) crimp cap with a (b) (4) and (b) (4) .

Bioburden and Endotoxin

Bioburden and endotoxin are measured as in-process controls (IPC) at the (b) (4) (b) (4) . Three consecutive production lots were evaluated for bioburden and endotoxin from process step (b) (4) " to (b) (4) (b) (4)

Bioburden results show that an initial bioburden of 33-95 CFU/mL at the (b) (4) (b) (4) before (b) (4) step decreased to 0 CFU/mL at the (b) (4) sampling step and maintained this level to final testing.

Endotoxin results were below the specification of (b) (4) /mL for all sample points for all lots manufactured.

Packaging and Labeling

Packaging and labeling occurs in Building (b) (4) a (b) (4) -story building. The labeling and packaging area on the second floor is currently licensed for the production of (b) (4) and (b) (4) . This area was inspected during the PAI of May/June 2008.

Lyophilization

There are (b) (lyophilizers that will be used for HFCP production, (b) (4) (b) (4) . They are located in Building (b) (4) The validation of the lyophilization process was conducted using both HFCP and Haemocomplettan P lots.

Equipment

All equipment has been qualified and is periodically requalified.

Utilities

The purified water system and the water for injection system are currently licensed for the manufacture of Humate-P® and were covered during the GMP inspection in March/April 2008.

For the HVAC systems, there were no 483 items from either the 2008 GMP inspection or the PAI inspection in May/June.

Cleaning Validation

Cleaning validations for major equipment were reviewed and found acceptable.

Conclusions

The DMPQ reviewer, Rebecca Olin, recommends approval of this submission.

4. Nonclinical Pharmacology/Toxicology

RiaSTAP™ was determined to be safe based on non-clinical studies (GLP and non-GLP) and its long-standing clinical history and use. Pre-clinical studies were conducted for local tolerance and neoantigenicity (rabbit and guinea pig), acute toxicity (mouse and rat), safety pharmacology/ pharmacodynamics and efficacy ((b) (4) rat sepsis model, porcine coagulopathy model), and pharmacokinetics (non-rodent) at doses ranging from the clinical dose and up to more than ten fold maximal clinical dose. The safety profile of RiaSTAP™ is sufficient to support BLA approval. There were slight immunogenic responses following RiaSTAP™ administration (dogs and rabbit) likely attributed to immune reaction to human protein which is not atypical with human biologic products. *In vitro* and *in vivo* mutagenesis and carcinogenesis studies have not been performed with RiaSTAP™. Previous experience with fibrinogen indicates a potential for clot formation and thromboembolic events when administered in pre-disposed patients and associated with elevated levels of fibrinogen in plasma.

The Pharm/Tox reviewer, La'Nissa Brown, recommends approval.

5. Clinical Pharmacology

A prospective, open label, uncontrolled, multicenter pharmacokinetic study was conducted in 5 females and 9 males with congenital fibrinogen deficiency (afibrinogenemia), ranging in age from 8 to 61 years (2 children, 3 adolescents, 9 adults). Each subject received a single intravenous dose of 70 mg/kg RiaSTAP. Blood samples were drawn from the patients to determine the fibrinogen activity at baseline and up to 14 days after the infusion. The pharmacokinetic parameters of RiaSTAP are summarized in Table 2.

No statistically relevant difference was observed between males and females for fibrinogen activity. Subjects less than 16 years of age (n=4) had shorter half-life (69.9 ± 8.5) and faster clearance (0.73 ± 0.14) compared to subjects >16 years of age. The number of subjects less than 16 years of age in this study limits statistical interpretations.

The incremental *in vivo* recovery (IVR) was determined from levels obtained up to 4 hours post-infusion. The median incremental IVR was 1.7 mg/dL (range 1.30 – 2.73 mg/dL) increase per mg/kg. The median *in vivo* recovery indicates that a dose of 70 mg/kg will increase patients' fibrinogen plasma concentration by approximately 120 mg/dL.

The pharmacokinetic analysis using fibrinogen antigen data (ELISA) was concordant with the fibrinogen activity (Clauss assay).

Table 2: Pharmacokinetic Parameters (n=14) for Fibrinogen Activity

Parameters	Mean ± SD (range)
Half-life [hours]	78.7 ± 18.13 (55.73-117.26)
C_{max} [mg/dL]	140 ± 27 (100-210)
AUC for dose of 70 mg/kg [mg*hr/mL]	124.3 ± 24.16 (81.73-156.40)
Clearance [mL/h/kg]	0.59 ± 0.13 (0.45-0.86)
Mean residence time [hours]	92.8 ± 20.11 (66.14-126.44)
Volume of distribution at steady state [mL/kg]	52.7 ± 7.48 (36.22-67.67)

The clinical pharmacology reviewer, Iftekhar Mahmood, recommends approval.

6. Clinical/Statistical-Efficacy

Executive Summary

Congenital afibrinogenemia is a rare coagulation disorder, usually with an autosomal recessive mode of inheritance. Based on the published prevalence, it is estimated that 150 to 300 patients suffer from afibrinogenemia in the US. It is characterized by bleeding manifestations that often start at birth with uncontrolled umbilical cord hemorrhages. Bleeding may occur after minor trauma or small surgical intervention into skin, mucosa, muscles, gastrointestinal tract or the brain.

Clinical symptoms of hypofibrinogenemia are usually milder compared with afibrinogenemia. The condition is frequently combined with a dysfibrinogenemia that is characterized with an abnormal fibrinogen variant (hypodysfibrinogenemia).

At the June 2005 Biological Therapeutics for Rare Plasma Protein Disorders Public Workshop the FDA stated that it would be open to discuss novel proposals for clinical development programs to facilitate approval of products intended to treat a rare plasma protein disorder. CBER negotiated the following clinical program to support the licensure of RiaSTAP intended for treatment of the rare coagulation disorder of congenital fibrinogen deficiency:

- A clinical study with a surrogate efficacy endpoint to support product approval.
- A post-approval efficacy study that confirms the surrogate endpoint data.

The pivotal study for the BLA, Study BI3023_2001, uses maximum clot firmness (MCF), as determined by thromboelastogram (TEG) as a surrogate endpoint to demonstrate hemostatic efficacy. RiaSTAP was found to be effective in increasing clot firmness in patients with congenital afibrinogenemia as measured by thromboelastometry. The pivotal study met its surrogate endpoint of a difference between the pre-infusion (i.e. just before infusion of RiaSTAP) and 1 hour post-infusion MCF values. The study demonstrated that the MCF at 1 hour after administration of RiaSTAP at a dose of 70 mg/kg was higher compared to baseline. The mean change from pre-infusion to 1 hour post-infusion was 8.9 mm in the primary analysis (9.9 mm for subjects < 16 years old and

8.5 mm for subjects > 16 to < 65 years old). The clinical significance of the change in MCF values from baseline to 1 hour post infusion is being evaluated in a Phase 4 study (B13023_3001) by assessing the correlation between MCF values and hemostatic efficacy. This post-marketing protocol has been submitted to study sites for institutional review board (IRB) approval to initiate the study.

- Study: ongoing
- Projected completion date: March 2014
- Final study report: September 2014

After administration of 70 mg/kg RiaSTAP, fibrinogen levels increased to the plasma levels as seen in the previous study 7MN-501FM and reported in the literature. *In vivo* recovery indicates that an average dose of 1 mg/kg fibrinogen is necessary to increase patient fibrinogen plasma concentration by approximately 1.5 mg/ml and thereby obtain normal levels.

Adverse events that were noted were not considered to be related to RiaSTAP. There were no deaths or adverse events that led to study discontinuation. Two subjects in study B13023_2001 experienced treatment-emergent adverse events (TEAE): epistaxis, gastro-esophageal reflux, headache, and pain. Of these, only one TEAE (headache) occurred within 72 hours of the end of infusion and was considered to be temporally associated with RiaSTAP administration. The other TEAEs occurred between 10 and 13 days after the end of infusion. No cases of viral transmissions have been reported. No patient experienced a thromboembolic event.

RiaSTAP is currently licensed in 12 European and Asian countries under the trade name Haemocomplettan® P. The following table summarizes the clinical studies conducted for RiaSTAP and Haemocomplettan® P:

Study	No of subjects	Study title and design	Treatment
B13023_3001 Ongoing: RiaSTAP 2008 onwards	23	A post marketing commitment study, historically controlled To validate an association between MCF the surrogate endpoint in study 2001 and clinical efficacy of stopping acute bleeding	Loading dose of 70mg/kg Subsequent dose (mg/kg) = [Target level(mg/dl-measured level (mg/dl)]/1.7 (mg/dL/mg/kg)
B13023_2001 (RiaSTAP): July 07- May 08	15	PK in congenital afibrinogenemia MCF as a surrogate efficacy endpoint	Single IV 70 mg/kg
CE1221-1 Haemocomplettan	100	A retrospective physician survey for	Patients received either Haemocomplettan P or

P 2002-2003		use as historical control for study B13023_3001	cryoprecipitate
7D-501FM Haemocomplettan P April 1991-June 1994	94	A clinical observational monitoring project in subjects with acquired fibrinogen deficiency	Dosage guided by physician assessment of individual therapeutic need
7MN-101FM April -Nov 1993 Haemocomplettan P	6	PK study	Single IV dose 70mg/kg
7MN-501FM Haemocomplettan P May 1985-Feb 1992	12	Retrospective phase IV to evaluate efficacy of Haemocomplettan P in congenital deficient patients including dysfibrogenemia	Adults 1-2 g Children 15-30 mg/kg Further infusions as needed.
7D-402XX-RS Haemocomplettan P June 85-June 87	6	Collection of additional viral safety data on subjects treated in earlier study	

Study BI3023_2001 was conducted according to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) recommendations. The other supportive studies were performed prior to these guidelines but were compliant with the Declaration of Helsinki. Written informed consent was obtained for all participants in all studies.

Protocol Study B13203_2001

Study 2001was conducted as a multinational, prospective, open-label, uncontrolled study. Each subject was to receive a single intravenous infusion of 70 mg/kg body weight (b.w.). Subjects were included if they were at least 6 years old and had documented congenital fibrinogen deficiency. All subjects had to be in a non-bleeding state. Plasma fibrinogen activity and antigen at screening had to be undetectable (i.e. <20 mg/dL) (i.e. afibrinogenemia).

Objectives and Endpoints

The primary objectives of the study were to compare maximum clot strength (MCF) as a surrogate marker for hemostatic efficacy before and after administration of RiaSTAP™ in subjects with congenital fibrinogen deficiency and to demonstrate that MCF 1 hour

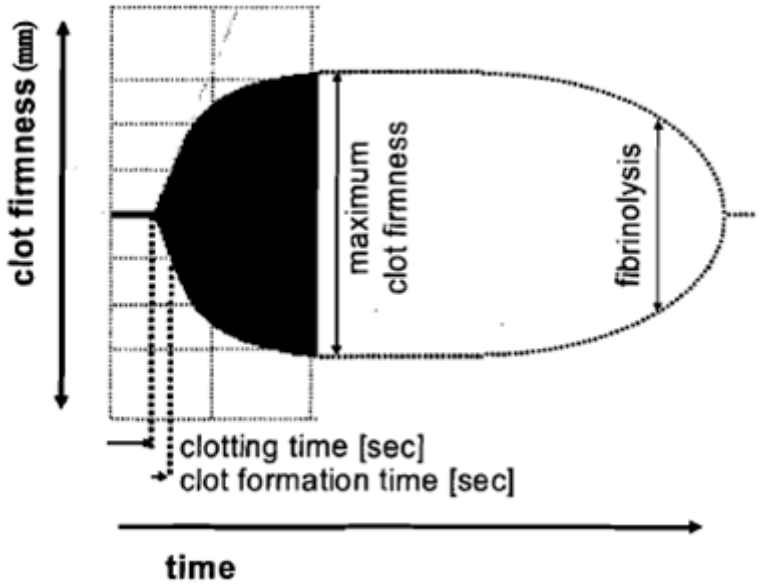
after administration of 70 mg/kg of the product is higher compared to baseline and to determine the single-dose pharmacokinetics of RiaSTAP™ in subjects with congenital fibrinogen deficiency.

The primary surrogate endpoint of the study was the difference between the pre-infusion (i.e. just before infusion of RiaSTAP™) and 1 h post-infusion MCF values. The statistical null hypothesis of no difference was tested against a two sided alternative hypothesis with a one sided sample t–test for paired observations. The maximum permitted type 1 error was 5%, two sided.

The secondary objective was to assess the safety of subjects with congenital fibrinogen deficiency especially with regards to thrombogenicity.

The efficacy variable measured in this study was the surrogate endpoint MCF, a functional parameter which depends on the activation of coagulation, the fibrinogen content of the plasma sample and the polymerization/crosslinking of the fibrin network. MCF was assessed at a central laboratory from frozen citrated plasma samples obtained prior to infusion and 1 hour (h) after the end of infusion. The change in MCF between pre-infusion and 1 h post infusion was the surrogate efficacy endpoint.

MCF was determined using TEG, a method for the continuous measurement of clot formation and clot firmness. It utilizes a mechanical detection system, which is based on the ability of the blood or plasma clot to form a mechanical coupling over a distance of 1 mm. A thromboelastogram (TEG) is the continuous registration of blood clot firmness during the entire coagulation process. In the literature TEG has been used as a functional marker for the assessment of fibrinogen content, and for the effects of fibrinogen supplementation on clinical efficacy. The sensitivity of TEG to fibrinogen supplementations of fibrinogen-deficient plasma has been shown using both commercially available deficient plasma, as well as using plasma from afibrinogenemic patients validated by CSL Behring (shown below).



Change in MCF (measured in mm) was analyzed for paired observations. The primary analysis was performed on the intention-to-treat (ITT) population and a secondary analysis was performed on the per-protocol (PP) population.

The rationale and justification for use of MCF as a parameter from TEG to serve as a surrogate endpoint

Historically, physicians used fibrinogen levels to manage coagulation in fibrinogen deficient patients. In recent years, the convenience of MCF testing has made it a more commonly used tool for this purpose. MCF is a functional parameter which depends on the activation of coagulation, the fibrinogen content of the sample (in plasma) and the polymerization/crosslinking of the fibrin network. MCF is determined using thromboelastography (TEG), a method for the continuous measurement of clot formation and clot firmness which utilizes a mechanical detection system based on the ability of the blood or plasma clot to form a mechanical coupling over a distance of 1 mm.

As MCF is the surrogate efficacy marker in this application, and published information on the direct correlation of MCF to fibrinogen levels is not available, CSLB performed an *in vitro* study to characterize a functional assay for circulating fibrinogen based on TEG (Kalina U; Blood Cog fibr). Thromboelastic clotting time and MCF were determined in normal human plasma pool, fibrinogen-deficient plasma pool, normal whole blood, and individual plasma samples from 17 subjects with fibrinogen deficiency using validated methods. Plasma samples spiked with varying concentrations of exogenous fibrinogen were also measured. Results were compared with Clauss assay (clotting assay designed to measure fibrinogen) and ELISA.

Over the tested range of 0 -3 mg/mL of added exogenous fibrinogen, the MCF standard curve for determination of fibrinogen in plasma pools was linear (r^2= 0.97). MCF was linearly correlated with both Clauss assay (r^2= 0.93) and ELISA (r^2= 0.95).

The platelet contribution to MCF could be effectively abolished by freezing, filtration, or addition of cytochalasin D. In unspiked plasma samples from individual subjects with fibrinogen deficiency, fibrinogen was undetectable by TEG. By all methods, the response to spiking with fibrinogen in such samples coincided closely in subjects with afibrinogenemia and hypofibrinogenemia. In dysfibrinogenemia, Clauss assay and clotting time responses to spiking were reduced, while the ELISA response was variable (Anderson L, Transfusion Medicine, 2006)

RESULTS OF PIVOTAL STUDY B13203_2001

Efficacy

15 subjects enrolled in the sites in US and Italy received RIASTAP. The population was 86.7% white, 5 subjects (33.3%) were female and 10 (66.7%) were male. The mean age was 30 years (range of 8 to 61 years; 73.3% of subjects were 16 to <65 years and 26.7% were 8 to 14 years).

The results of the surrogate endpoint are shown in the table below (as per sponsor's analysis):

MCF in mm in ITT population

Time point	N	Mean ± SD	Median (range)	Q_{25}	Q_{75}	P-value[a]
Pre-infusion	13	0 ± 0	0 (0-0)	0	0	--
1 hour post-infusion	13	10.3 ± 2.7	10.0 (6.5-16.5)	8.5	12.0	--
Mean change (primary analysis)	15[b]	8.9 ± 4.4	9.5 (0-16.5)	7.0	12.0	<0.0001

ITT = intention-to-treat; MCF = maximum clot firmness; Q_{25} = 25% quartile; Q_{75} = 75% quartile; SD = standard deviation.

[a] 2-sided p-value from one-sample t-test.

[b] The mean change was set to 0 for 2 subjects with missing MCF data.

[b] MCF set at 0 in two subjects with missing MCF data

MCF in mm by sex in ITT population

Time point	Males (N=10)		Females (N=5)	
	Mean ± SD	Median (range)	Mean ± SD	Median (range)
Pre-infusion	0 ± 0	0 (0-0)	0 ± 0	0 (0-0)
1 hour post-infusion	9.9 ± 1.9	10.0 (6.5-12.5)	11.0 ± 4.2	10.3 (7.0-16.5)
Mean change (primary analysis)	9.0 ± 3.6	9.8 (0-12.5)	8.8 ± 6.1	8.5 (0-16.5)

No differences in MCF values were seen between males and females.

MCF in mm by age in ITT population

Time point	<16 years (N=4)		≥16 to <65 years (N=11)	
	Mean ± SD	Median (range)	Mean ± SD	Median (range)
Pre-infusion	0 ± 0	0 (0-0)	0 ± 0	0 (0-0)
1 hour post-infusion	9.9 ± 4.6	8.3 (6.5-16.5)	10.4 ± 1.6	10.5 (8.0-12.5)
Mean change (primary analysis)	9.9 ± 4.6	8.3 (6.5-16.5)	8.5 ± 4.5	10.0 (0-12.5)

There was no relevant difference between the 2 age groups in the mean change from pre-infusion to 1h post infusion.

Analysis of Fibrinogen activity by MCF at one hour shows a linear correlation (r^2= .85).

In conclusion, the findings of this study demonstrated an increase in the surrogate efficacy parameter MCF in congenital deficient patients (any increase from baseline which was 0 in all patients). The PK results obtained in 14 subjects (PK per Protocol population) showed an incremental IVR of 1.7 mg/dL increase per mg/kg for fibrinogen activity and a half life of 78±18.3 h. These results are consistent with those reported in a previous PK study in 5 subjects (Study BI3.023I7MN-101FM and literature reports).

STUDY B13023_3001 PHASE 4 FOR VALIDATION OF THE SURROGATE ENDPOINT

This study is ongoing and being conducted as a multinational, multicenter, prospective, open, historically controlled, non-inferiority post-marketing study.

The primary objectives of the study are:

1. To demonstrate the efficacy of fibrinogen concentrate, RiaSTAP, by adequately controlling acute bleeding (spontaneous or after trauma) compared to the hemostatic efficacy data in the historical control on cryoprecipitate treatment from a retrospective survey. Trauma for the purposes of the study is defined as any accidental event (e.g. fall, cut with a sharp object, blow to the head) leading to an acute bleeding. Treatment starts only after the accidental event.
2. To evaluate an association between the overall clinical assessment of hemostatic efficacy and the surrogate endpoint "clot strength" (referred to as MCF in this protocol), also termed "clot firmness", that was used as a surrogate endpoint for hemostatic efficacy, and was determined via TEG in the pivotal pharmacokinetic study BI3023_2001 MCF will be determined prior to and 60 minutes after the end of every infusion.
3. To elevate fibrinogen plasma levels 60 minutes post infusion to a peak target level of 100 mg/dL with an accepted lower limit of 80 mg/dL for minor events (e.g. epistaxis, intramuscular bleeding, menorrhagia), and to a peak target level of 150 mg/dL with an accepted lower limit of 130 mg/dL for major events (e.g. head trauma, intracranial bleeding).

Dosing:

Dosing will be individually calculated for each subject based on the: target plasma fibrinogen level based on the type of bleeding, measured actual plasma fibrinogen level and body weight. The injection rate is not to exceed 5 mL per minute (100 mg/minute).

The dose is calculated based on the following formula:

$$\frac{\text{[Target level (mg/dL) - measured level (mg/dL)]}}{\text{1.7 (mg/dL per mg/kg body weight)}}$$

Study population:

Approximately 30 study centers, in the U.S. and EU, will participate. Twenty-three (23) evaluable subjects requiring on-demand treatment for acute bleeding either spontaneous or after trauma, will be enrolled. The historical control group will consist of 39 subjects treated with cryoprecipitate after at least one acute episode of bleeding. This data will be taken from the study survey CE1221_1 conducted by the sponsor.

The subjects included in the study must have: a documented congenital fibrinogen deficiency, with plasma fibrinogen activity at screening < 50 mg/dL, and fibrinogen antigen at screening < 1.2 times the plasma fibrinogen activity at screening, and presenting with an episode of acute bleeding (either spontaneous or after trauma). Subjects requiring surgery will be excluded from the study.

Statistical Methodology:

The primary variable of efficacy is the investigator's overall hemostatic efficacy assessment based on a four point ordinal scale (excellent, good, poor, none), to be assessed 24 hours after the last RiaSTAP infusion or on Day 14 (whichever is earlier).

A test for non-inferiority of RiaSTAP treatment compared to cryoprecipitate (obtained from physician survey Study CE122l_l) will be performed. Due to the rarity of the disease and limitation of the sample size, the non-inferiority margin was set at 30%.

To show whether a change in MCF values correlate with the physician rating of excellent and good (predefined in the protocol). The physician will not be aware of the MCF values for the patients. The analyses of MCF will be performed for subjects in the ITT population and subjects in the PP population. Only data from the RIASTAP study will be used for analysis of this co-primary endpoint

Sixty minutes after infusion of RiaSTAP, MCF values (mean, SD, median, and range) will be obtained as both absolute and changes from baseline.. Mean changes in MCF will be described with two-sided 95% CIs. MCF values will also be evaluated and presented graphically.

The same analyses will be performed separated for the predefined subgroups as well as separated for the subjects' clinical outcome represented by each step of the 4-point hemostatic efficacy scale (excellent, good, poor, none) and the dichotomized hemostatic efficacy scale (excellent/good, poor/none). Scatterplots will be presented to show MCF by hemostatic efficacy outcome. To evaluate the correlation between MCF and the primary efficacy variable Spearman correlation coefficients will be estimated between the 4-point hemostatic efficacy with MCF and MCF change.

The clinical reviewer, Nisha Jain, recommends approval of this BLA.

7. Safety

Safety Monitoring In Study B13023_2001

Safety assessments included adverse events (AEs), physical examinations and vital signs, laboratory assessments (hematology, biochemistry, and thrombogenicity), and viral monitoring that included testing for HIV-1 and 2, HAV, HBV, HCV, and B19 virus. Viral serology was checked at baseline using enzyme immunoassays for HIV-1 and 2, HAV, HBV, HCV and B19 antibodies. At 3 months after the infusion anti HIV1 and 2, HAV, HCV, HBV and HBsAg were determined. PCR assessments evaluated HIV-1, HAV, HBV, HCV and B19 at baseline, for B19 at day 10 and HAV day 14.

Studies to Support Clinical Trials

Safety data are available from the pivotal study B13023 2001, and post-marketing experience in Europe since 1986 is also available.

- An open-label, uncontrolled, prospective Phase 1 study (Study 7MN-I0IFM) conducted between April and November 1993.

- A retrospective Phase 4 study (Study 7MN-501FM) conducted between May 1985 and February 1992.

- Additional virus safety data are available from an earlier study conducted in subjects with congenital fibrinogen deficiency (Study 7D-402XX-RS) conducted between June 1985 and June 1987.

- A few reports of safety events are available from a retrospective clinical survey (Clinical Survey CE1221_1, henceforth referred to as the clinical survey) conducted between October 2002 and March 2003.

In the five clinical studies, a total of 39 patients have been exposed to the product.

Pivotal Study B13023_2001

There were 4 treatment-emergent AEs (TEAEs) (epistaxis, gastroesophageal reflux disease, headache, and pain) reported by 2 subjects in this study. All the TEAEs occurred between 2 and 13 days. All TEAEs were mild and not related to study medication except for one (headache) that occurred within 72 hours after infusion. None of the TEAEs were serious or led to discontinuation from the study. Changes in the laboratory parameters for signals of thrombogenecity such as d-dimers, fibrinopeptide1 and 2 are not clinically relevant. There were no reports of viral seroconversion in any patients.

Study 7MN-101FM

6 subjects were enrolled in the study. 6 AEs were observed in 4 subjects shown in the table below:

Subject number	Adverse event	Intensity	Causality
(b) (6)	Dyspnea	Mild	Possibly related
	Elevated temperature	Mild	Possibly related
	Pain along the infused vein	Mild	Not related
	Headache	Mild	Not related
	Pallor, nausea, shivering	Moderate	Not related
	Dizziness, blood pressure 110/70 mmHg	Mild	Possibly related

Study 7MN-501FM

12 subjects were treated in this study. A reversible anaphylactic reaction with severe hypotension, cyanosis of lips and extremities, abdominal pain, and pain in the back was reported in one subject.
1 SAE was reported for a subject with afibrinogenemia who developed venous thrombosis and non-fatal lung embolism after treatment outside of the study.
The patient was being treated for a “collum femoris” fracture and received heparin treatment.

Study 7D-402XX-RS

This study was primarily a viral safety study. Six subjects were evaluated for viral seroconversion. No subject seroconverted.

Deaths

No deaths were reported in the pivotal study and the supportive studies 7MN-101FM, 7MN-501FM, and 7D-402XX-RS.

POST-MARKETING ADVERSE EVENT DATA IN EUROPE

CSL Behring has received a total of 48 adverse event reports for Haemocomplettan P since it began marketing in Europe (1986-2008), corresponding to one report for every 3,414 doses distributed over this time period.

Overview of ADRs reported 1986-2008:

Adverse drug reaction	Number of cases	Sponsor Causality	FDA Causality Assessment
Allergic/anaphylactoid reactions	20	16 possibly related 3 insufficient information 1 unlikely	All possibly related
Thromboembolic events	9 1 acquired, 8 congenital deficiency	8 possibly related 1 insufficient data	All possibly related
Suspected viral transmission	14 (12 acquired and 2 in congenital deficiency)	13 unrelated, 1 insufficient data	Agrees with the sponsor
Lack of effect	3	2 insufficient data, 1 unrelated	Insufficient information to assess
Leucocytosis	1	unrelated	unrelated
Lung infiltration	1	unrelated	unrelated

[a] FDA considers a case of bone pains and chills, identified as unexpected by the sponsor, to be an allergic reaction and related

PHARMACOVIGILANCE

The pivotal clinical studies assessing the efficacy and safety of RiaSTAP were restricted in size, limiting the ability to detect uncommon adverse events. Additionally, the population receiving the product post-licensure may differ from the population studied in pre-approval trials. In the European experience, a total of 48 adverse events were reported for Haemocomplettan P since it began marketing in 1986, corresponding to one report for every 3,414 doses distributed.

The sponsor has complied with providing a detailed line list of all adverse events, including thromboembolic events and viral transmission. Gender, age, indication for treatment, dose level and number of doses, time interval from treatment to onset of adverse event, description of events, concomitant medications and surveillance methods by which these adverse events were collected. The data is complete.

The sponsor has also supplied complete safety reports and Periodic Safety Update Reports as requested.

The RiaSTAP™ Pharmacovigilance plan, per ICH E2E Pharmacovigilance Planning guidance is provided as requested. The Pharmacovigilance plan summarizes and addresses safety concerns, includes identified potential risks, describes routine FDA compliant pharmacovigilance practices and includes additional post-marketing actions.

The sponsor supplied data on clinical investigations conducted in Europe for the indication of acquired hypofibrinogenemia, as requested.

A complete and thorough pharmacovigilance plan was supplied in the amendment. Included in the pharmacovigilance plan is a description of routine pharmacovigilance activities, as well as a description of post-marketing signal detection. Safety concerns and detailed action plans are addressed.

The pharmacovigilance reviewer (Faith Barash) concludes that all concerns have been addressed and she recommends approval.

8. Advisory Committee Meeting

The Blood Products Advisory Committee met on January 9, 2009. The FDA asked the committee to respond to the following questions:

1. With regard to safety and efficacy:
    a. Is the safety profile acceptable?
    b. Did the study show that the MCF increase was significant and likely to be clinically meaningful?

2. Is the phase 4 study adequately designed:
    a. to verify the clinical benefit of the product?
    b. to determine whether the surrogate endpoint correlates with a meaningful clinical endpoint?

A majority of the committee answered “yes” to all of the questions.

9. Pediatrics

This submission did not trigger PREA because of Orphan Drug status.

RiaSTAP studies have included subjects below the age of 16 years. In the pharmacokinetic study, 2 children (8 and 11 years), 3 adolescents (12, 14 and 16 years), were studied. Subjects less than 16 years of age (n = 4) had shorter half-life (69.9 ± 8.5h) and faster clearance (0.7 ± 0.1 mg/L) compared adults (half-life: 82.3 ± 20.0h, clearance: 0.53 ± 0.1 mg/L). The number of subjects less than 16 years of age in this study limits statistical interpretation.

10. Other Relevant Regulatory Issues

Financial Disclosure

In Section 1.3.4 of the original BLA submission regarding Certification: Financial Interests and Arrangements of Clinical Investigators, the sponsor has checked the following as true:

"As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I also certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

11. Labeling

The package insert, vial label and carton label have been reviewed by FDA and are acceptable. There is no need for instructions for patients since the product will be administered only under the supervision of a physician.

12. Recommendations/Risk Benefit Assessment

The CBER review committee unanimously recommends approval of this BLA. There are currently no concerns regarding the risk/benefit ratio.

RiaSTAP, Fibrinogen Concentrate (human) is recommended for approval under the accelerated approval process. The product is intended to treat serious and life threatening condition, acute bleeding in patients with congenital fibrinogen deficiency. RiaSTAP provides a reasonably likely therapeutic benefit by showing an increase in maximum clot firmness (MCF), a functional measure of fibrinogen. The clinical benefit is being verified in an ongoing phase 4 study that evaluates hemostatic efficacy based on a predefined rating scale.

<u>POST MARKETING REQUIREMENTS</u>

Products approved under the accelerated approval regulations, 21 CFR 601.40 - 46, require further adequate and well-controlled confirmatory clinical studies to verify and describe clinical benefit. These commitments, along with any completion dates agreed upon, are listed below:

1. The sponsor agreed to conduct a Phase 4 study B13023_3001 to verify the clinical benefit by comparing the hemostatic efficacy of RiaSTAP to historical control. This

study is designed as a multinational, multicenter, prospective, open, historically controlled, non-inferiority post-marketing study.

- Study: ongoing
- Projected completion date: March 2014
- Final study report: September 2014

Postmarketing Commitments subject to reporting requirements of 21 CFR 601.70

These commitments, along with any completion dates agreed upon, are listed below.

2. The sponsor has committed to evaluate efficacy and safety in the peri-operative period in patients with congenital fibrinogen deficiency:

Protocol submitted:	within six months after approval
Study initiated:	within three months of submission of final protocol to CBER
Projected study completion:	within five years of study initiation
Final study report:	within six months of study completion

3. The sponsor has committed to evaluate efficacy and safety for routine prophylaxis in patients with congenital fibrinogen deficiency.

Protocol submitted:	within six months after approval
Study initiated:	within three months of submission of final protocol to CBER
Projected study completion:	within five years of study initiation
Final study report:	within six months of study completion

We are requesting that the sponsor submit clinical protocols to their IND, with a cross-reference letter to this biologics license application (BLA). Nonclinical and chemistry, manufacturing, and controls protocols and all study final reports should be submitted to the BLA.

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, the sponsor must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted), and
- explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment).