



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Final Review Memo:

TO: STN 125317/0

SPONSOR: CSL Behring

PRODUCT: Fibrinogen concentrate (human) pasteurized

FROM: Nisha Jain, M.D., Clinical Review Branch, HFM-392

SUBJECT: Final review of the BLA (STN 128317)

TO: Vasantha Kumar, Regulatory Project Manager, HFM-380

THROUGH: Basil Golding, M.D., Director, Division of Hematology HFM-392

CHAIRPERSON: Laura wood

RECOMMENDATION:

RIASTAP was found to be effective in increasing clot firmness in patients with congenital afibrinogenemia as measured by thromboelastometry. The pivotal study B13023_2001 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.

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

patients 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. 2 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.

POST MARKETING REQUIREMENT:

The BLA was submitted under the Accelerated Approval procedure. The pivotal study for the BLA, Study No. B13023_2001, uses maximum clot firmness (MCF), as determined by thromboelastometry as a surrogate endpoint to demonstrate hemostatic efficacy. The assay for MCF as determined by thromboelastometry, using a method that abolishes platelet function, and measures clot firmness or strength (maximal amplitude of the clot in mm.) was validated by the sponsor as a measure of fibrinogen function *in vitro*. FDA accepted MCF as a surrogate marker that would likely predict clinical outcomes during treatment of bleeding episodes in patients with congenital fibrinogen deficiency. The surrogate endpoint will be validated by showing a correlation between MCF and clinical efficacy in a post-marketing Phase 4 study (Study No. B13023_3001). 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

EXECUTIVE SUMMARY

The BLA contains data provided by CSL Behring GmbH (Germany), from a PK study that also evaluated MCF as a surrogate to demonstrate hemostatic efficacy and safety to support approval of RIASTAP™, Fibrinogen Concentrate (Human) pasteurized, for treatment in patients of congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia).

RIASTAP™ is administered at the initial dose of 70 mg/kg body weight. Estimated subsequent doses are calculated based on the formula described below

$$\begin{aligned} \text{Estimated subsequent dose (mg/kg body weight)} \\ = \frac{[\text{Target level (mg/dL)} - \text{measured level (mg/dL)}]}{1.7 \text{ (mg/dL per mg/kg body weight)}} \end{aligned}$$

The injection rate is not to exceed 5 mL per minute (100 mg/minute).

REVIEW RESPONSIBILITIES:

Product and Chairperson:	Laura Wood Roman Drews (viral safety)
Medical:	Nisha Jain, M.D.
Statistician:	Boris Zaslavsky
RPM:	Vasanth Kumar
BIMO:	Christine Draback
OCBQ:	
APLB:	Katherine Miller

TRADE NAME:

The trade name RIASTAP has been approved by APLB.

ORPHAN DRUG STATUS:

Orphan drug status granted in March 2008

PREA:

Exempt from PREA because of orphan drug status

FINANCIAL DISCLOSURE:

Financial disclosure statements have been submitted in the application.

INDICATION SOUGHT:

"Fibrinogen Concentrate, pasteurized, is indicated for the treatment of congenital fibrinogen deficiency."

REGULATORY HISTORY:

The following summarizes the regulatory chronology of this BLA:

June 2002:	First Pre-IND meeting with CSL Behring (known at the time as Aventis Behring) held. A retrospective physician survey (Clinical Survey CE1221_1) was suggested to gather information concerning bleeding frequency and treatments for fibrinogen deficiency which could also be used as a historical control.
June 2005:	Biological Therapeutics for Rare Plasma Protein Disorders Public Workshop held. Clinical development programs to support approval of therapies to treat rare plasma protein disorders were discussed

- September 2005: OBRR representatives stated that “ in order to facilitate approval of products for small markets, the Agency would be open to discuss proposals for clinical development programs” and recommended the following: A clinical study with a surrogate efficacy endpoint to support product approval and post-approval efficacy study that confirms the surrogate endpoint data (i.e. Accelerated Approval).
- May 2006: A follow-up meeting was held with the FDA to discuss the proposed clinical program for HFCEP with the indication "Treatment of acute bleeding in patients with congenital fibrinogen deficiency". At this meeting, the FDA agreed to the proposed Accelerated Approval clinical program. CSL Behring would submit a BLA with data from a PK study (Study 2001) and MCF as measured by TEG as a surrogate endpoint, together with previous clinical studies, post-marketing surveillance data, and a clinical survey conducted in response to CBER's comments during the 21 June 2002 meeting to demonstrate safety and efficacy in the proposed indication.
- November 2006: IND submitted (BB-IND (b)(4)) with the PK and evaluation of MCF a surrogate endpoint for hemostatic efficacy.
- January 2007: CBER notified CSL that the study may proceed.
- July 2007: The post-marketing protocol to validate the surrogate endpoint was submitted to CBER
- March 2008: Orphan drug status granted
- July 17 2008: BLA submitted

INTRODUCTION:

FIBRINOGEN

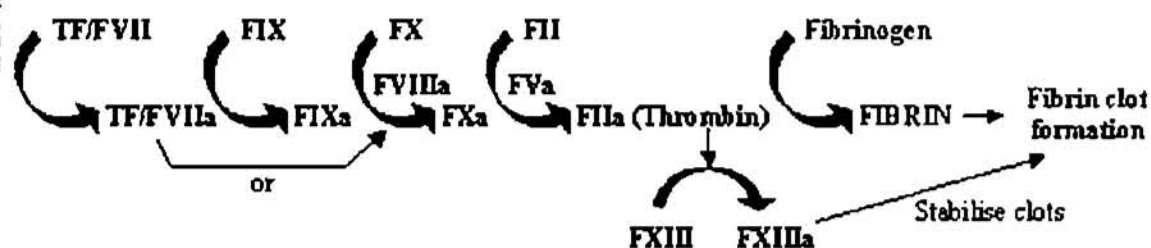
Fibrinogen was first isolated from horse plasma by Hammarsten in 1876, although an inactive precursor to fibrin was proposed to exist as early as 1859 by Deni de Commercy.

Fibrinogen is a plasma glycoprotein synthesised in the liver that is essential for hemostasis wound healing, fibrinolysis, inflammation, angiogenesis, cellular and matrix interactions, and neoplasia. These processes involve the conversion of fibrinogen to fibrin, and often the interaction of fibrinogen with various proteins and cells. Normal plasma levels are about 2.5 g fibrinogen/L of blood, however, concentrations of fibrinogen can increase by as much as 200-400% during times of physiological stress (primarily due to the actions of macrophage-derived interleukin-6, an acute phase reactant).

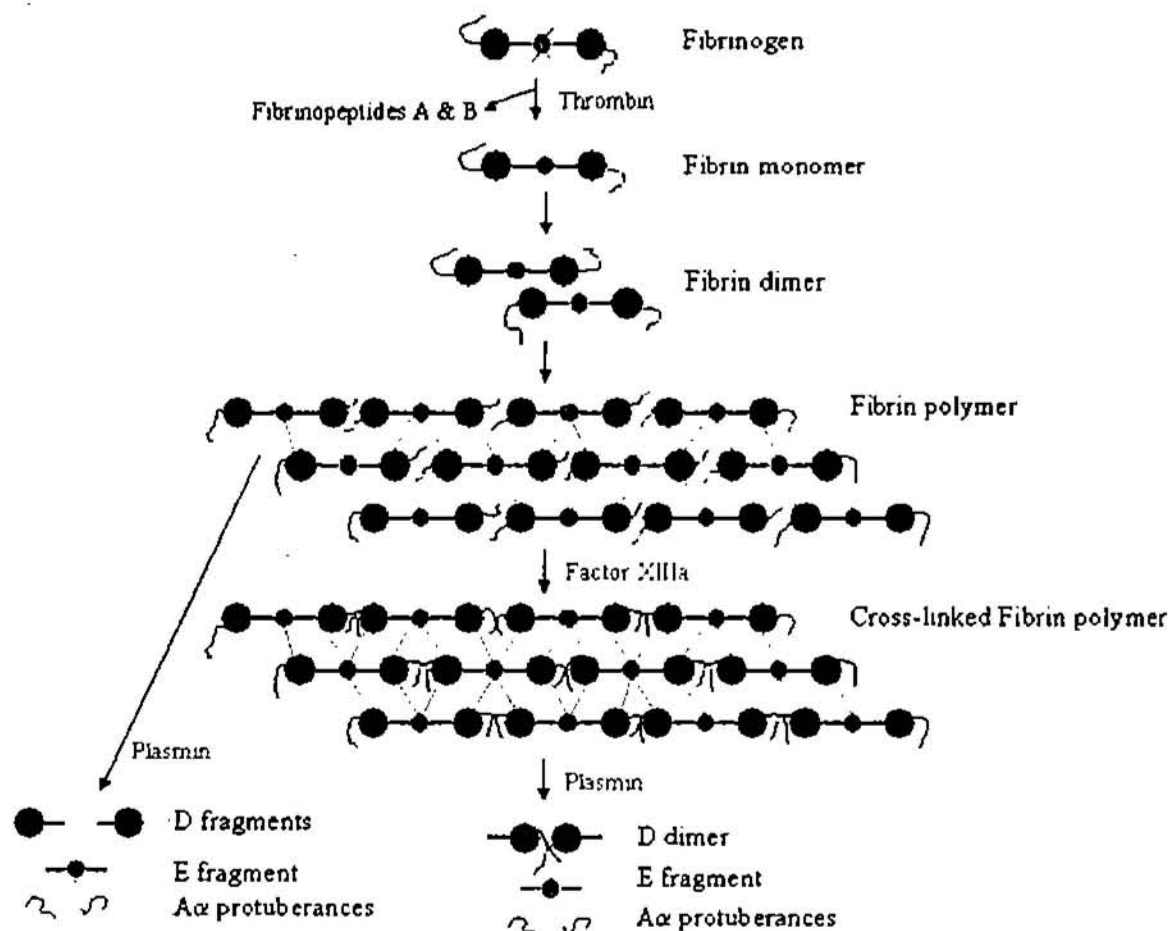
Fibrinogen is a large, complex glycoprotein composed of three pairs of polypeptides: two $A\alpha$, two $B\beta$, and two γ . These polypeptides are linked together by 29 disulphide bonds. The polypeptides are oriented so all six N-terminal ends meet to form the central E domain. Two regions of coiled coil alpha helices stretch out on either side of the E domain, each consisting of one $A\alpha$, one $B\beta$ and one γ polypeptide. Each coiled coil region ends in a globular D domain consisting of the C-terminal ends of $B\beta$ and γ , as well as part of $A\alpha$. The C-terminal end of $A\alpha$ then protrudes from each D domain as a long strand; these $A\alpha$ protuberances can interact with each other and with the E domain during fibrin clot cross-linking. Both the E and D domains contain important binding sites for the conversion of fibrinogen to fibrin, for fibrin assembly and cross-linking, and for platelet aggregation. Bound calcium ions are important to help maintain the structure of fibrinogen.

The N-terminal ends of both the $A\alpha$ and $B\beta$ polypeptides are cleaved by thrombin in order to turn soluble fibrinogen into gel-forming fibrin. Once cleaved from fibrinogen, the N-terminal ends are known as fibrinopeptide A (from $A\alpha$ polypeptide) and fibrinopeptide B (from $B\beta$ polypeptide). The removal of fibrinopeptides A and B from the N-terminal ends of $A\alpha$ and $B\beta$ exposes 'knobs' on the E domain, which can interact with the 'holes' always present on the D domains. Fibrin molecules can link together through the interaction of the E domain on one fibrin molecule to the D domains on four other fibrin molecules, thereby polymerising to form staggered oligomers that build up into protofibrils. As the fibrin oligomers aggregate, these protofibrils continue to lengthen to make long fibres that can wind around one another to make multi-stranded, thick bundles, which can branch into a 3-dimensional network of entangled fibres, the fibrin clot. The fibrin clot is then stabilised by Factor XIIIa.

Role of fibrinogen in coagulation cascade: adapted from the Protein data bank



Fibrin Polymerisation and lysis: The knobs on the E domain bind the holes on up to four D domains (grey lines), forming a long fibrous latticework. The clot is then stabilized through cross-linking.



CONGENITAL FIBRINOGEN DEFICIENCY:

The concentration of fibrinogen circulating in normal plasma ranges from 2.0 to 4.5 g/L however, in patients with various congenital or acquired conditions, the levels of clottable fibrinogen are markedly reduced or undetectable [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).

Congenital afibrinogenemia is a rare coagulation disorder usually with an autosomal recessive mode of inheritance. Based on the published prevalence, it is estimated that 150-300 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. The causative mutation for congenital afibrinogenemia has recently been reported as a homozygous 11-kb deletion of the A α gene. The majority of patients have truncating mutations in the A α gene, but the involvement of mutations in all three fibrinogen genes could be implicated and their presence cannot be excluded as causative factors. It has been recently reported that missense mutations in the B β fibrinogen gene could cause congenital afibrinogenemia by impairing fibrinogen secretion.

Clinical symptoms of hypofibrinogenemia are usually milder compared with afibrinogenemia, and the condition is frequently combined with a dysfibrinogenemia that is characterized with an abnormal fibrinogen variant (hypodysfibrinogenemia). Several missense mutations in the three fibrinogen genes have been identified as the cause of dysfibrinogenemia and hypofibrinogenemia that lead to abnormal gene expression resulting in the decreased fibrinogen concentration or dysfunctional fibrinogen molecules.

REGULATORY BACKGROUND

FIBRINOGEN

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 was also used 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. Several fibrin sealants, containing fibrinogen are currently licensed in the U.S., but no fibrinogen for intravenous use is licensed.

CSL Behring GmbH and its predecessors have been producing 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 in 1985, coinciding with significant improvements in purity and safety, particularly with regard to the implementation of a heat-treatment step to inactivate viruses. 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 stabilizers are from plasma collected at U.S. licensed facilities.

At the June 2005 Biological Therapeutics for Rare Plasma Protein Disorders Public Workshop the Agency 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 BLA was submitted under the Accelerated Approval procedure. The pivotal study for the BLA, Study No. B13023_2001, uses maximum clot firmness (MCF), as determined by thromboelastogram (TEG, APPENDIX 3), as a surrogate endpoint to demonstrate hemostatic efficacy. The surrogate endpoint will be validated by showing an association between MCF and clinical efficacy in a post-marketing study (Study No. B13023_3001). This post-marketing protocol has been submitted to study sites for institutional review board (IRB) approval to initiate the study,

RIASTAP™ is currently licensed in 9 European countries under the trade name Haemocomplettan® P. For the US market, RIASTAP™ will be used as the trade name. RIASTAP was granted Orphan Drug Designation for "treatment of fibrinogen deficient patients" on 13 March 2008.

LIST OF STUDIES CONDUCTED:

Study	No of subjects	Study title and design	Treatment
B13023_3001 Ongoing: RIASTAP 2008 onwards	23	A postmarketing commitment study, historically controlled To validate an association between MCF the surrogate endpoint in study 2001 and clinical efficacy of stopping	Loading dose of 70mg/kg Subsequent dose (mg/kg) = [Target level(mg/dl-measured level (mg/dl)]/1.7(mg/dL/mg/kg)

		acute bleeding	
B13023_2001 (RIASTAP): July 07- May 08	15	PK in congenital fibrinogenemia MCF as a surrogate efficacy endpoint	Single IV 70 mg/kg
CE1221-1 Hemocomplettan P 2002-2003	100	A retrospective physician survey for use a shistorical control for study 13023_3001	Patients received either Hemocomplettan P or cryoprecipitate
7D-501FM Hemocomplettan 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 Hemocomplettan P	6	PK study	Single IV dose 70mg/kg
7MN-501FM Hemocomplettan P May 1985-Feb 1992	12	Retrospective phase IV to evaluate efficacy of hemocompelttan in congenital deficaint patienst including dysfibrogenemia	Adults 1-2 g Children 15-30 mg/kg Further infusions as needed.
7D-402XX-RS Hemocomplettan P June 85-June 87	6	Collection of additional viral safety data on subjects treated in earlier study	

Study B13023_2001 was conducted according to the International Conference on Harmonisation (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.

SYNOPSIS OF PROTOCOL FOR STUDY B13203_2001

Study 2001 was 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

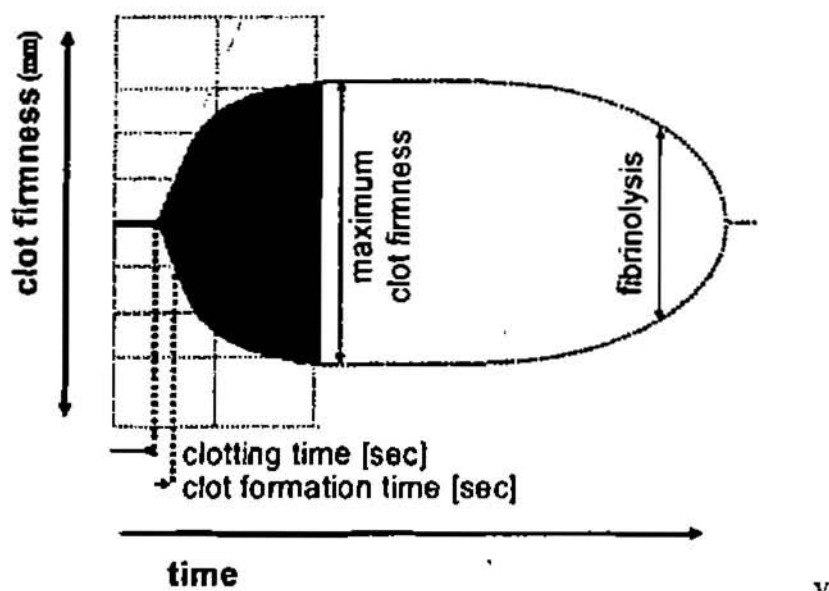
The primary objectives of the study were to compare maximum clot strength (MCF) as a surrogate marker for hemostatic efficacy before and after administration of RIASTAP™ in subjects with congenital fibrinogen deficiency and to demonstrate that MCF 1 hour after administration of 70 mg/kg of the product 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 (as presented by the sponsor):

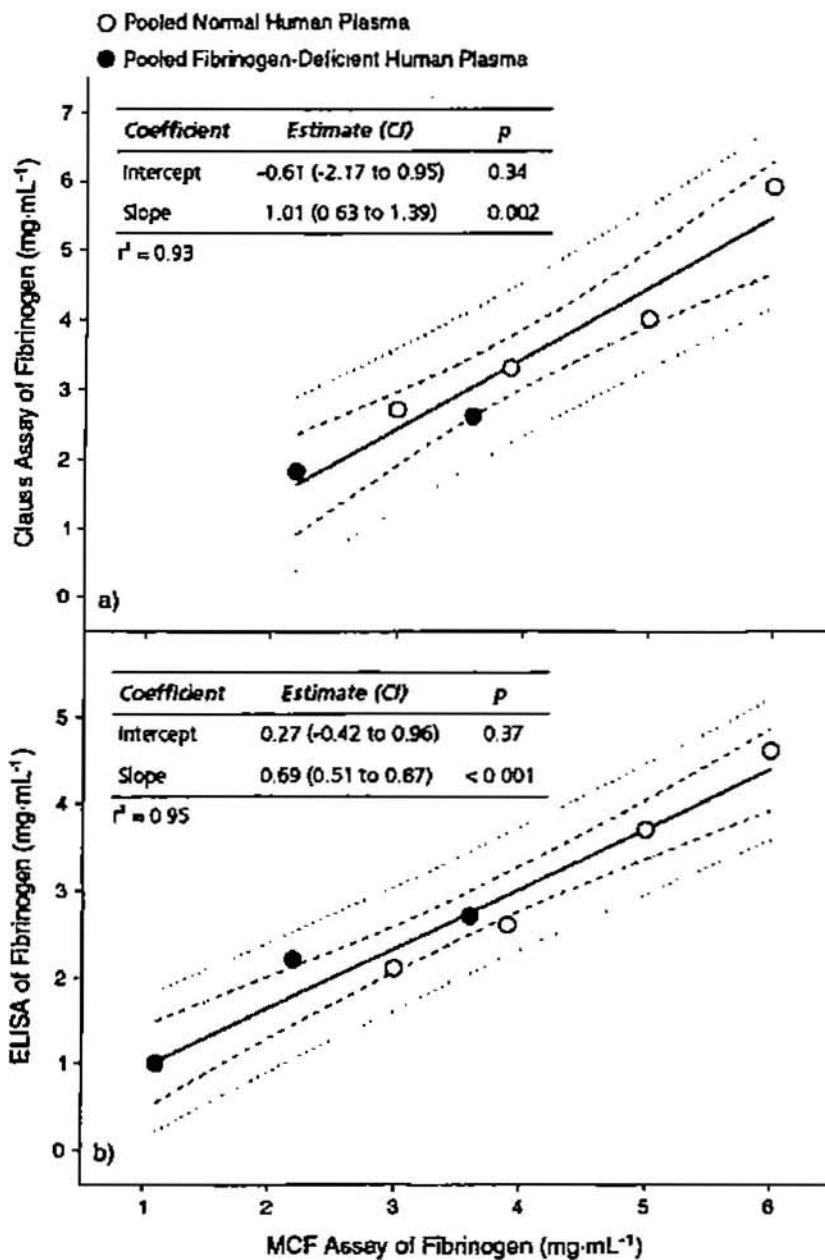
Historically, physicians used fibrinogen levels to manage coagulation in fibrinogen deficient patients. In recent years, the convenience of MCF testing has made it a more commonly used tool for this purpose. MCF is a functional parameter which depends on the activation of coagulation, the fibrinogen 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 ($r^2 = 0.95$) (See APPENDIX 3)

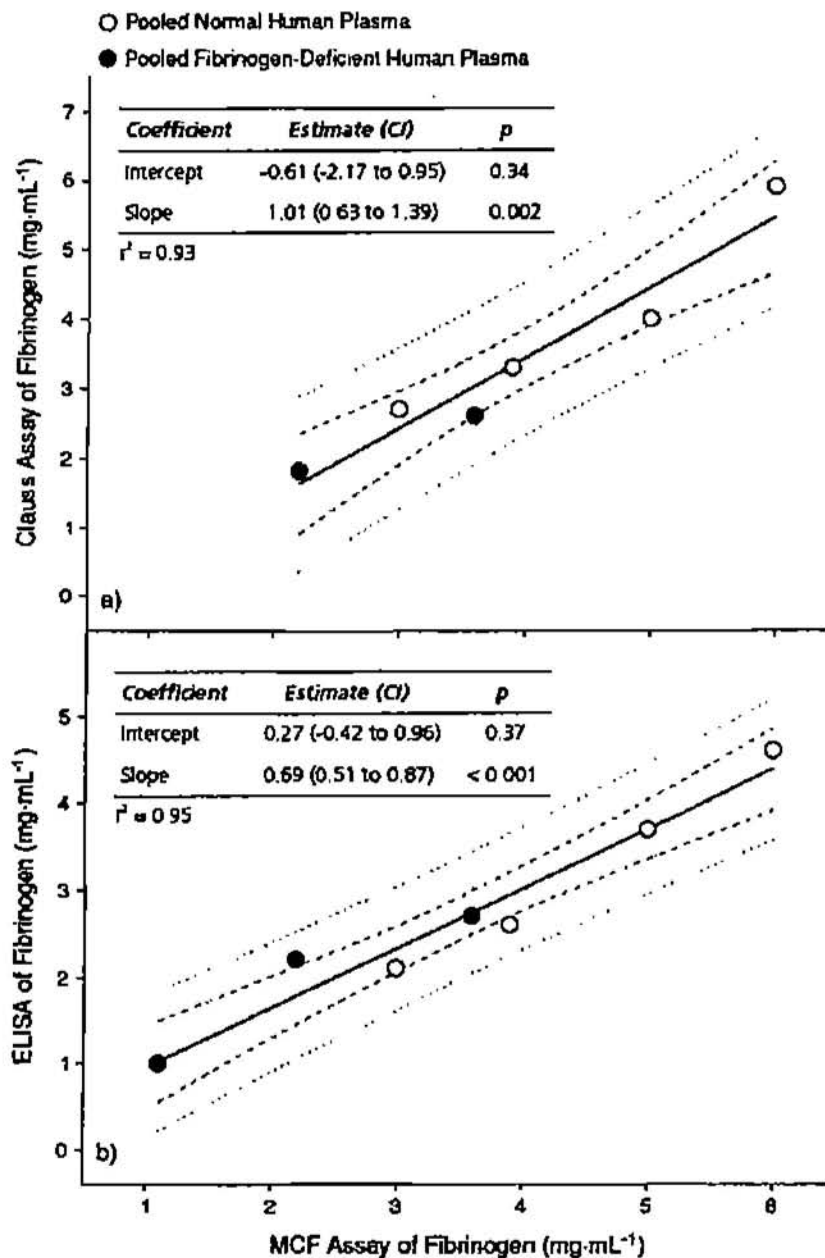
The platelet contribution to MCF could be effectively abolished by freezing, filtration, or addition of cytochalasin D. In unspiked plasma samples from individual subjects with fibrinogen deficiency, fibrinogen was undetectable by TEG. By all methods, the response to spiking with fibrinogen in such samples 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)

Linear regression analysis of fibrinogen concentrations^a determined by thromboelastographic MCF assay – Clauss assay and ELISA

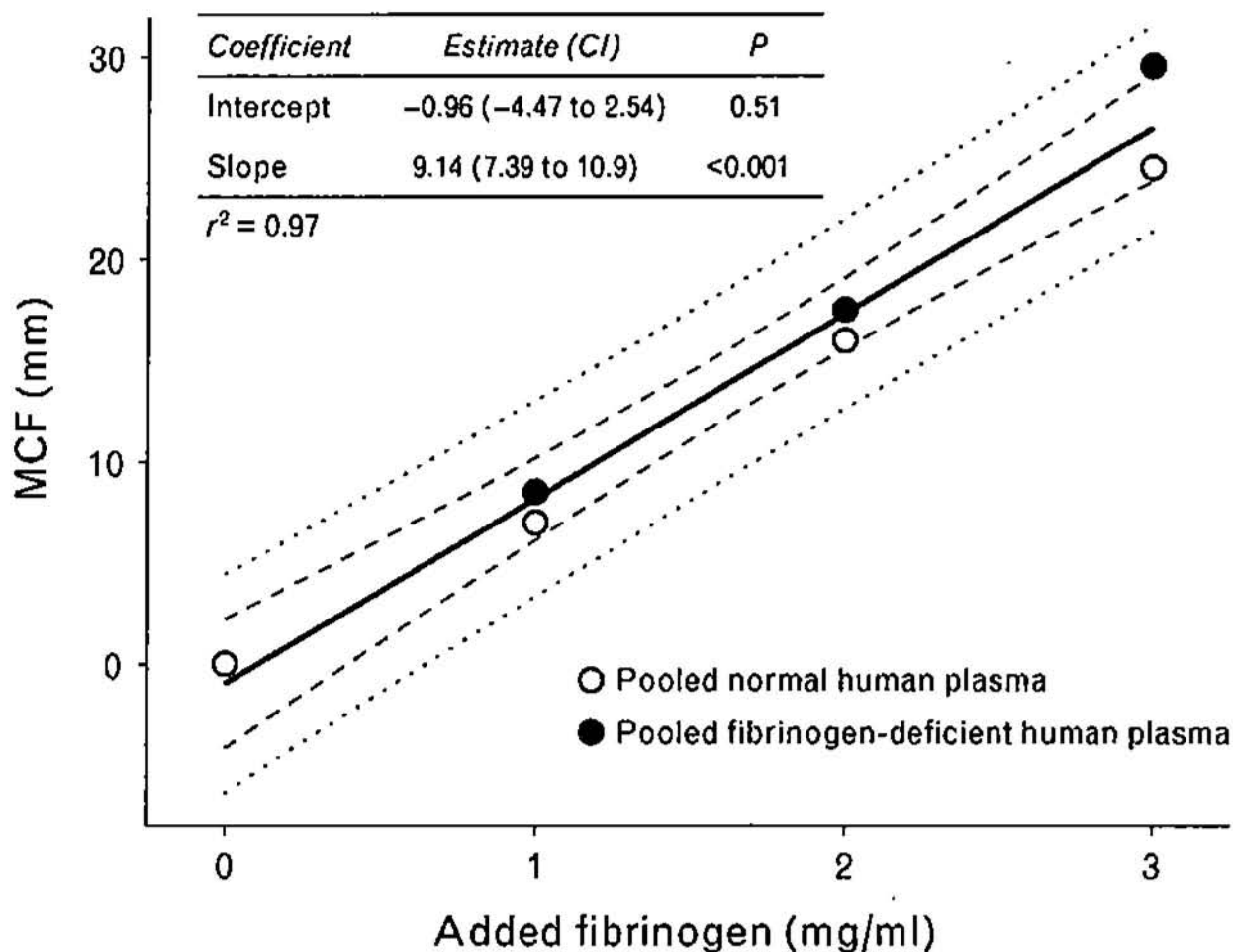


^a Exogenous fibrinogen (0, 1, 2 or 3 mg/mL) was added to normal human plasma or fibrinogen-deficient human plasma.

Linear regression analysis of fibrinogen concentrations^a determined by thromboelastographic MCF assay – Clauss assay and ELISA



^a Exogenous fibrinogen (0, 1, 2 or 3 mg/mL) was added to normal human plasma or fibrinogen-deficient human plasma.



Standard curve constructed by linear regression analysis with MCF on y axis and added fibrinogen (0, 1, 2, or 3mg/ml) on the x axis. Fibrinogen was added to normal pooled plasma (open circles) or fibrinogen deficient plasma (closed circles). MCF without added fibrinogen was subtracted from values of pooled normal plasma.

SAFETY MONITORING

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.

RESULTS OF PIVOTAL STUDY B13203_2001

PHARMACOKINETIC

See Dr. Mahmood's memo

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; Q₂₅ = 25% quartile; Q₇₅ = 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 difference was MCF values were seen between males and females.

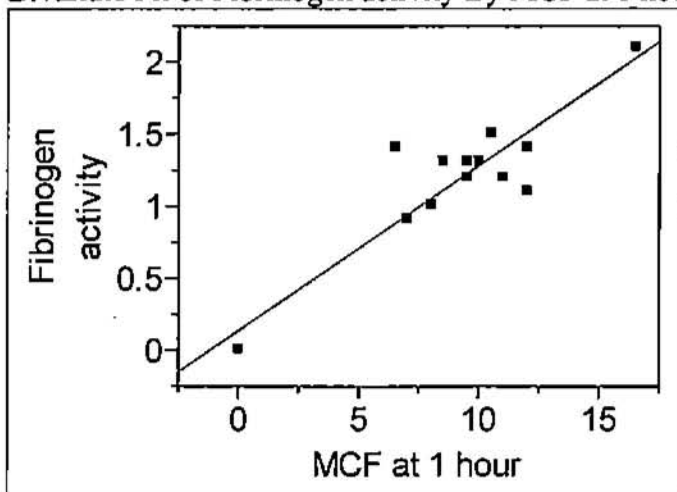
MCF in mm by age in ITT population

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 ($r^2 = .85$).

Bivariate Fit of Fibrinogen activity By MCF at 1 hour



Linear Fit

Fibrinogen activity = $0.1304189 + 0.1148375 \times \text{MCF at 1 hour}$

Summary of Fit

RSquare	0.847794
RSquare Adj	0.836086
Root Mean Square Error	0.215686
Mean of Response	1.133333
Observations (or Sum Wgts)	15

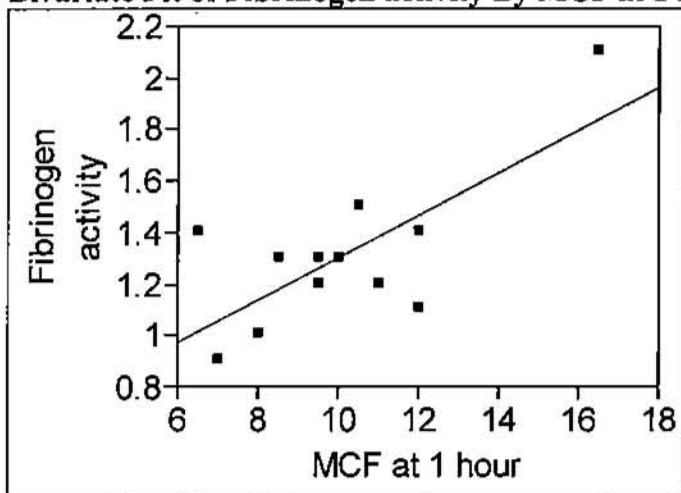
Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	3.3685676	3.36857	72.4105
Error	13	0.6047658	0.04652	Prob > F
C. Total	14	3.9733333		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob> t
Intercept	0.1304189	0.130354	1.00	0.3353
MCF at 1 hour	0.1148375	0.013495	8.51	<.0001

II) Per protocol

Bivariate Fit of Fibrinogen activity By MCF at 1 hour

— Linear Fit

Linear Fit

Fibrinogen activity = $0.4839709 + 0.0817433 \times \text{MCF at 1 hour}$

Summary of Fit

RSquare	0.525849
RSquare Adj	0.482744
Root Mean Square Error	0.208573
Mean of Response	1.307692
Observations (or Sum Wgts)	13

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.5307029	0.530703	12.1994
Error	11	0.4785278	0.043503	
C. Total	12	1.0092308		

Prob > F 0.0050

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob> t
Intercept	0.4839709	0.242828	1.99	0.0717
MCF at 1 hour	0.0817433	0.023404	3.49	0.0050

Safety Analysis

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 thrombogenicity such as d-dimers, fibrinopeptide1 and 2 were not clinically relevant. There were no reports of viral seroconversion in any patient.

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).

SUPPORTIVE STUDIES FOR SAFETY AND EFFICACY

STUDY CE122CL: CLINICAL SURVEY STUDY

This multinational clinical survey was conducted between October 2002 and March 2003 in 10 countries (US, Italy, Canada, Austria, Iran, Germany, Spain, Switzerland, Turkey, and the United Kingdom) to collect data on the current treatment modalities used by physicians in the treatment of subjects with congenital fibrinogen deficiency. It consisted of a questionnaire that collected information under two parts:

General

- number of patients treated, plasma fibrinogen levels needed for hemostasis, duration of treatments, laboratory assays used to measure fibrinogen levels, and types of products used for on-demand and prophylaxis treatment

Patient-specific

- Physicians-recorded specific information on demographics, schedule and type of treatment and details of each event

Safety parameters not recorded in this questionnaire.

Data from 31 physicians and 100 patients (53 men and 47 women, median age 20.5 years, range 7 days to 75 years) were included in the analysis. In this survey, physicians reported primarily two types of treatment: fibrinogen concentrate and cryoprecipitate (data from the US was primarily on use of cryoprecipitate as fibrinogen concentrate is not licensed in the US). In one center use of fresh frozen plasma, coagulation factors VIIa and VIII concentrates was reported.

70% of the patients had levels less than 10 mg/dL, 28% had levels between 10 and 50 mg/dL and 1% had more than 50 mg/dL and 1% had missing data.

Of the 100 subjects affected with either afibrinogenemia or hypofibrinogenemia and bleeding symptoms, 81 subjects were treated on-demand, 19 subjects had been under routine prophylactic treatment for a total of 517 events (483 under on demand and 34 under routine prophylaxis treatment). The hemostatic efficacy rating for both cryoprecipitate and fibrinogen was excellent/good for 90% of the events.

Peak plasma levels were recorded for only a limited number of events (30 bleeding episodes, 20 surgeries, and 26 traumas).

The median annual incidence of bleeding/trauma episodes was 0.0 bleeds for subjects on prophylactic replacement therapy (range 0 to 2.6) and 0.2 for subjects on on-demand therapy (range 0 to 16.5 bleeds).

Of the 100 subjects only 39 received treatment with cryoprecipitate for \geq one bleeding episode and had hemostatic data available.

In conclusion, based on the physicians' assessment of efficacy, it appeared that both treatments were equally effective. It seems that the only advantage Fibrinogen Concentrate has over cryoprecipitate is its lower potential for viral transmission.

	Fibrinogen (N)	Cryo precipitate(N)	Either (N)	Other (N)
Type of Rx (subjects)				
On demand; N=81	24	10	42	5*
Prophylaxis; N=19	19	0	0	0
No of events; N=517				
On demand; N=483	248	201	8	18-FFP,3-FVIII
Prophylaxis; N=34	34			5 unknown
Hemostatic efficacy	N=248	N=173		N=22
Excellent	45%	36%		32%
Good	50%	54%		68%
Overall	94%	94%		100%

Study 7MN-501FM

This multicenter, conducted as Phase 4 study in Europe was performed between May 1985 and February 1992. It was designed as a retrospective data collection for safety and efficacy of fibrinogen concentrate when administered for treatment of bleeding in subjects with congenital fibrinogen deficiency (afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia).

Subjects received Hemocomplettan® P as a single i.v. infusion (adults at a dose of 1 to 2 g, children at a dose of 15 to 30 mg/kg b.w.); further infusions were administered as required. The treatment duration varied from 1 day to 77 months (median 26.5 months), covering one or more hemorrhagic events, surgical interventions, or prophylactic substitutions. The age of the subjects ranged from 1 day to 29 years. Eight subjects were classified as suffering from afibrinogenemia, 3 subjects had hypofibrinogenemia, and 1 subject had dysfibrinogenemia combined with hypofibrinogenemia.

Clinical efficacy was evaluated in 26 bleeding events (hemorrhage into muscles or joints, hypermenorrhea, minor or intermediate injury, gastrointestinal bleeding) and 11 surgical interventions (osteosynthesis, pylorotomy, dental surgery, tonsillectomy, dissection of abscess, herniotomy, fixation of spinal cord). 89 infusions for prophylactic purposes were recorded, 86 of which were given to a single subject. The clinical efficacy was estimated as good in all 26 bleeding episodes and in 10 of 11 surgical interventions. In 1 case (a subject with pylorotomy), the efficacy was judged as moderate.

The response (rise of fibrinogen plasma concentration per dose/kg.) was calculated from values obtained in 8 subjects before and 30 -60 minutes after the end of the infusion. The median increase (i.e. the incremental IVR) of 1.5 mg/dL, (range 0.8 -2.3 mg/dL) was similar to that seen in the pivotal study B13023_2001 .

STUDIES TO SUPPORT SAFETY

Safety data are available from the pivotal study B13023 2001 and from post-marketing experience in Europe since 1986 is also available. Please note that fibrinogen concentrate has been licensed in Europe since 1986 under the trade name of Hemocomplettan P. In the US, the tradename of the product will be RIASTAP.

- An open-label, uncontrolled, prospective Phase 1 study (Study 7MN-I0IFM) conducted between April to 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 thrombogenicity 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. 6 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

Post marketing thromboembolic events in Europe (1986-2008)

The cases of thromboembolism occurred in both congenital and acquired fibrinogenemia. In 8/9 cases were congenital deficient patients. Of the 8, 4 received prophylactic treatment. Time between the last infusion of RIASTAP and the event was 10, 3, 15 and missing respectively for the 4 patients. Only the event that occurred 3 days after the infusion can be considered as related to the product. 3/8 patients received treatment on demand: 23 year old 1gm of Hemocomplettan P and 4.5 g of another fibrinogen concentrate at same time (multiple arterial thrombosis due to massive overdose), 32 year old received 2g every other day x 3 weeks for a subdural hematoma, 32 year old with iatrogenic arterial injury received 8g single dose. In one patient who experienced TE, the type of treatment was not reported.

41	CD afib	-	Dosed for 2 yrs (2 g every 7-14 days)	3 days	Central retinal vein thrombosis	-
39	CD afib, hx or ICH	Hand paresis	Prophylactic dosing for 15 yrs (6 g every 2 wks)	10 days	Small thrombosis of aortic arch/mild CVA	-
18	CD afib	Implanted infusaport	Prophylactic dosing for many yrs; dose increased for surgical procedure	15 days post-op	SC/jugular thrombosis	-
23	CD afib	-	1 g total dose	NA	Multiple arterial thromboses	4.5 g of another fibrinogen concentrate
32	CD afib	-	On-demand tx for massive hemorrhage after iatrogenic arterial injury (8-g single doses)	NA	Massive proximal DVT/ successfully treated	-
69	CD hypfib	Hematoma and hemorrhage/ AML	Not reported	48 hrs	Micro-vascular thrombosis	Aprotinin (i.v. and infusion)
32	CD afib	-	On-demand tx for large SDH (2 g every other day for 3 wk)	3 wks	Pulmonary embolus/ recovered	-

Viral seroconversion:

Post marketing reports in Europe of suspicious viral transmission (1986-2008)

Age (yrs)	Indication for treatment	Time between HFC Dose and Event	Lab Event (year)	Co-suspect Plasma/Blood Products/Events
40	CD dysfib	9 yrs. from 1 st dose	Anti-HCV+ (1995)	Non-virus inactivated products
61	AD, cardiac surgery	10 mos. from dosing	Anti-HCV+ (1995)	Plasma, PRBCs
NA	AD, gynecologic surgery	Hep C dx immediately after surgery	Anti-HCV+ (1988)	No baseline test done
68	AD, hemorrhagic shock	5 yrs. from dosing	HBsAg+ and HBcAg+ (1996)	5 U plasma, 14 U PRBCs
NA	AD, chemotherapy	NA	HCV- (1994)	PRBCs, platelets
40	AD, heart surgery	NA (treated in 1996)	HCV- (NA)	Platelets
22	AD, chemotherapy for ALL	11 mos.	Hep B+ (1997)	26 U PRBCs, 29U platelets, immunoglobulin, ATIII, human albumin from 06/96 to 08/97
71	AD, hip surgery	21 mos. from dosing	HCV- (1997)	PRBCs, PCC for massive intraoperative bleeding
10	AD, chemotherapy for ALL	26 mos. from last dose in 04/94	HCV+ (06/96) (HCV neg in 05/96)	PRBCs, platelets
NA	AD, surgery	Reported 14 yrs. from dosing	HCV+ (NA)	Plasma, patient was a nurse
28	AD, C-section	4 mos. from dose on 12/31/01	Hep B serology consistent with older infection (03/02)	PRBCs, plasma, human albumin
49	NA	NA	HCV+ (NA)	Multiple other blood products
NA	CD	NA	HCV+ (NA)	Plasma
44	AD, DIC/multiple trauma	25 to 37 mos. from single dose on 11/01	HCV- (2004)	PRBCs, platelets, ATIII

STUDY B13203_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 B13023-2001 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:

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

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 CE1221_1) 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.