

FDA Briefing Document
Blood Products Advisory Committee Meeting
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RIASTAP™ [Fibrinogen concentrate (Human)]

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1.0 GENERAL INFORMATION

PRODUCT NAME

Established name: Fibrinogen Concentrate (Human)

Proposed trade name: RIASTAP™

PRODUCT COMPOSITION (from the applicant's proposed label)

RIASTAP™ is a purified, pasteurized, lyophilized preparation of fibrinogen derived from human plasma. It is manufactured from cryoprecipitate into a glycine precipitate, which is then further purified by multiple precipitation/adsorption steps. The labeled amount of RIASTAP™ is 1 g of fibrinogen. When reconstituted, each vial contains 900 to 1300 mg fibrinogen, 400 to 700 mg human albumin, 375 to 660 mg L-arginine hydrochloride, 200 to 350 mg sodium chloride and 50 to 100 mg sodium citrate. Sodium hydroxide and hydrochloric acid may have been used to adjust the pH.

All plasma used in the manufacture of RIASTAP™ is tested using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to Human Immunodeficiency Virus (HIV)-1/2 and Hepatitis C Virus (HCV). Additionally, the plasma is tested with FDA-licensed Nucleic Acid Testing (NAT) for HCV and HIV-1 and found to be non-reactive (negative). For Hepatitis B Virus (HBV), an investigational NAT procedure is used; however, the significance of a negative result has not been established. In addition, the plasma has been tested by NAT for Hepatitis A Virus (HAV) and Parvovirus B19 (B19). Only plasma that passed virus screening is used for production, and the limit for B19 in the fractionation pool is set not to exceed 10^5 IU of B19V DNA per mL.

The manufacturing process has been demonstrated to reduce the risk of virus transmission (Appendix 4) in an additive manner: pasteurization (60°C for 20 hours), cryoprecipitation, and other absorption/precipitation steps have been validated in a series of *in vitro* experiments for their capacity to inactivate or remove a wide range of viruses of diverse physicochemical characteristics including: HIV, HAV, B19, West Nile Virus (WNV), Herpes Simplex Virus

type 1 (HSV-1), and the following model viruses: Bovine Viral Diarrhea Virus (BVDV) as a model virus for HCV and Canine Parvovirus (CPV) as a model virus for B19. Moreover, since its licensure in Europe in 1985, there has not been any proven viral transmission to patients related to the use of this product.

MANUFACTURER: CSL Behring GmbH (Germany)

PROPOSED INDICATION: RIASTAP™, Fibrinogen Concentrate (human) is indicated for the treatment of congenital fibrinogen deficiency

DOSING REGIMEN: Dosing will be individually calculated for each subject based on the: target plasma fibrinogen level, type of bleeding, measured actual plasma fibrinogen level and body weight. The dose will be calculated based on the following formula:
$$\frac{[\text{Target level (mg/dL)} - \text{measured level (mg/dL)}]}{1.7 \text{ (mg/dL per mg/kg body weight)}}$$

ROUTE OF ADMINISTRATION: Intravenous

POTENCY: Labeled as 1 g lyophilized fibrinogen in a single-use vial for reconstitution with 50 mL Sterile Water for Injection. Each vial contains 900-1300 mg fibrinogen and 400-700 mg human albumin. The actual fibrinogen potency in mg/vial for each lot is printed on the vial label.

2.0 EXECUTIVE SUMMARY

This briefing document contains a summary of data provided by CSL Behring GmbH (Germany), including safety and pharmacokinetics (PK) data, and a pivotal study using a surrogate endpoint. FDA agreed that the regulatory pathway for approval could invoke the Accelerated Approval process (APPENDIX 1) which allows the use of a surrogate endpoint in cases of serious and life threatening diseases. Thus, the pivotal study combined PK and safety evaluations with data that measured Maximum Clot Firmness (MCF) by thromboelastometry (ROTEM) (See APPENDICES 2 and 3) as a surrogate endpoint for clinical efficacy. MCF was performed to demonstrate functional activity of replacement fibrinogen when RIASTAP was administered in a manner known to provide a target fibrinogen level. A successful outcome of this study would support licensure of RIASTAP™, Fibrinogen Concentrate (Human) pasteurized, for treatment of patients with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia). The Accelerated Approval process requires that a subsequent Phase 4 study be performed to show that the surrogate endpoint correlates with a meaningful clinical outcome, i.e., hemostasis. The Phase 4 study should be ongoing prior to approval.

Dosing will be individually calculated for each subject based on the: target plasma fibrinogen level, type of bleeding, measured actual plasma fibrinogen level, and body weight. The dose is calculated based on the following formula:

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

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

The BLA contains data from the following completed studies described in the table below in reverse chronological order. Studies B13023_2001, B13023_3001 and CE1221_1 are studies conducted under a U.S. IND to support the indication. Additional studies conducted in Europe are supportive for safety and efficacy in the proposed indication.

Please note: In this document for studies conducted to support U.S. licensure the trade name RIASTAP™ will be used and for studies that supported the licensure in Europe Hemocomplettan P will be used.

Table Showing all Efficacy and Safety Studies

Study	No of subjects	Study title and design	Treatment
B13023_3001 Ongoing: RIASTAP 2008 onwards, U.S. IND, Phase 4.	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	Dosing will be individually calculated for each subject based on the: target plasma fibrinogen level, the type of bleeding, measured actual plasma fibrinogen level, and body weight
B13023_2001 (RIASTAP): July 07- May 08, U.S. IND, pivotal	15	PK in congenital afibrinogenemia MCF as a surrogate efficacy endpoint	Single IV 70 mg/kg
CE1221_1 Hemocomplettan P 2002-2003 Europe, control for U.S. Phase 4	100	A retrospective physician survey for use as historical control for study 13023_3001	Patients received either Hemocomplettan P or cryoprecipitate
7MN-101FM April -Nov 1993 Hemocomplettan P, Europe, supportive	6	PK study	Single IV dose 70mg/kg
7MN-501FM Hemocomplettan P May 1985-Feb 1992 Europe, supportive	12	Retrospective Phase 4 to evaluate efficacy of Hemocomplettan P in congenital deficient patients including dysfibrinogenemia	Adults 1-2 g Children 15-30 mg/kg Further infusions as needed.
7D-402XX-RS Hemocomplettan P June 85-June 87, Europe, supportive	6	Collection of additional viral safety data on subjects treated in earlier study	

Study B13023_2001 was conducted under US IND (–(b)(4)) according to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) recommendations. The other supportive studies were not performed under a US IND and were conducted prior to these guidelines, but were compliant with the Declaration of Helsinki. Written informed consent was obtained for all participants in all studies.

2.1 EFFICACY

The pivotal study, B13023_2001, was performed under Accelerated Approval, and provided data regarding PK, safety, and MCF, a surrogate marker for efficacy. In this study the incremental *in vivo* recovery (IVR) was determined by a functional assay, Clauss assay (see APPENDIX 4) from levels obtained up to 4 hours post-infusion. The median incremental IVR was 1.7 mg/dL (range 1.3 – 273 mg/dL) with a mean of 1.8 mg/dL increase per mg/kg body weight. No statistically relevant difference was observed between males and females for fibrinogen activity. The PK findings for fibrinogen activity after infusion with a single dose of 70 mg/kg of RIASTAP™ and the incremental *in vivo* recovery (IVR) were similar to the previous study 7MN-101FM. Fibrinogen given to subjects less than 16 years of age (n = 4) had a shorter half-life (69.9 ± 8.5 h) and faster clearance (0.73 ± 0.14 mg/dL) compared to subjects > 16 years of age. The number of subjects less than 16 years of age in this study limits statistical interpretations. In Study B13023_2001, the PK analysis using fibrinogen antigen data (ELISA) were concordant with those for fibrinogen activity (Clauss assay).

The 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 intent to treat analysis (N = 15, 9.9 mm for subjects < 16 years old and 8.5 mm for subjects > 16 to < 65 years old). The mean change of MCF by per protocol analysis was 10.3mm (N = 13). The normal MCF range for pooled plasma was 14-30 mm. The mean change in MCF values closely approximated the levels expected from adding known amounts of fibrinogen to plasma *in vitro*. 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.

2.2 SAFETY

Adverse events that were noted in the pivotal study were not considered to be related to RIASTAP™. There were no deaths or adverse events that led to study discontinuation. Two subjects in the pivotal experienced four 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 were reported in this study. No patient experienced a thromboembolic event.

2.3 CONCLUSION

RIASTAP™ was found to be effective in increasing clot firmness in patients with congenital afibrinogenemia as measured by thromboelastometry. 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. The median *in vivo* recovery indicates that an average dose of 70 mg/kg increase patients' fibrinogen plasma concentration by 120 mg/dL which exceeds the minimal hemostatic levels of 100 mg/dL (normal range 200-450 mg/dL). The safety profile appears to be acceptable.

3.0 INTRODUCTION AND BACKGROUND

3.1 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.

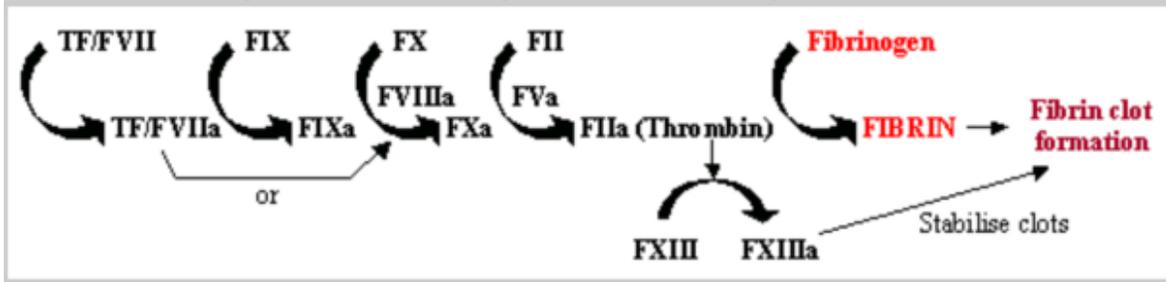
Fibrinogen is a plasma glycoprotein synthesized in the liver that is essential for hemostasis wound healing, fibrinolysis, inflammation, angiogenesis, cellular and matrix interactions, and neoplasia. These processes involve the conversion of fibrinogen to fibrin, and often the interaction of fibrinogen 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 α , two B β , 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 α , one B β and one γ polypeptide. Each coiled coil region ends in a globular D domain consisting of the C-terminal ends of B β and γ , as well as part of A α . The C-terminal end of A α then protrudes from each D domain as a long strand; these A α 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.

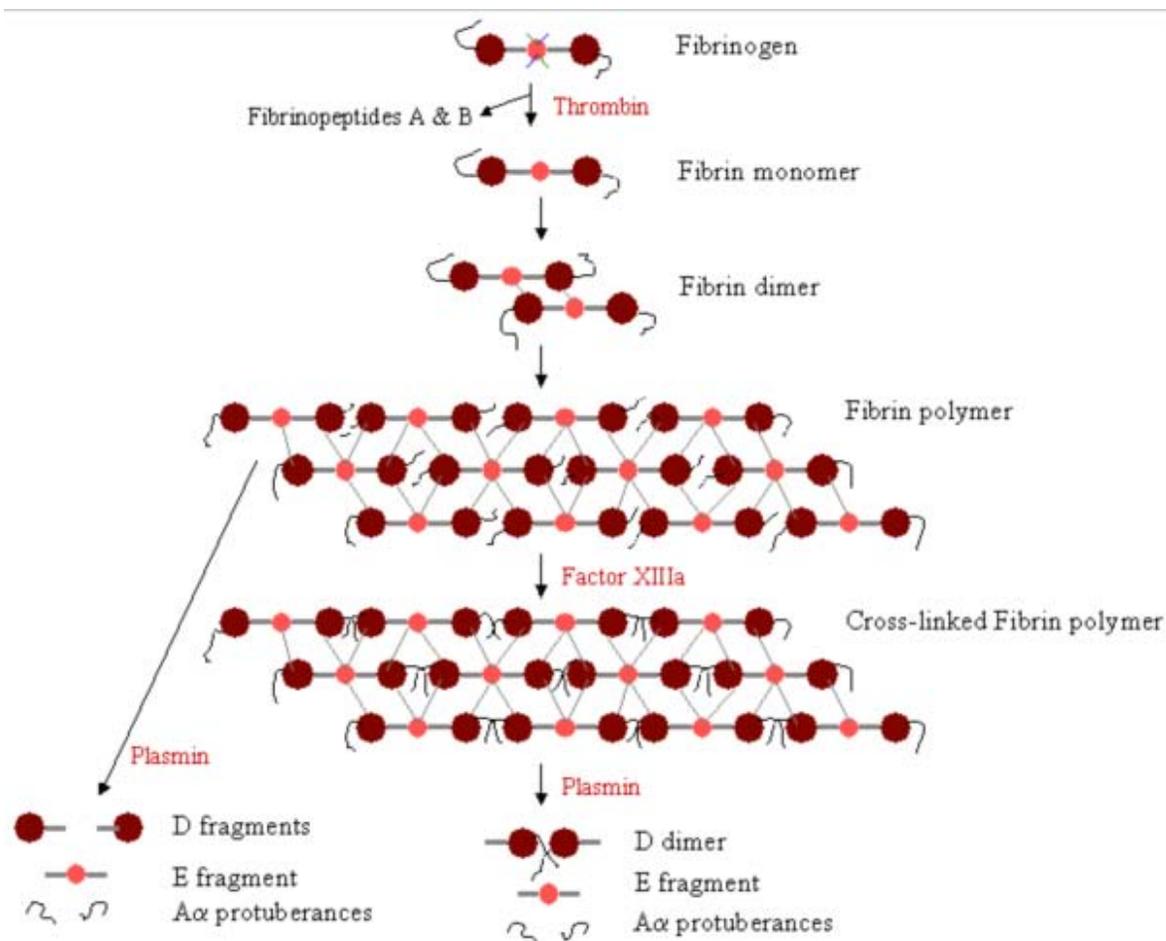
The N-terminal ends of both the A α and B β polypeptides are cleaved by thrombin in order to turn soluble fibrinogen into gel-forming fibrin. Once cleaved from fibrinogen, the N-terminal ends are known as fibrinopeptide A (from A α polypeptide) and fibrinopeptide B (from B β polypeptide). The removal of fibrinopeptides A and B from the N-terminal ends of A α and B β 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.

The role of fibrinogen in the blood 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.



Adapted from: Transfusion and Apheresis Science: Volume 32, Issue 3, June 2005, Pages 247-253

3.2 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 U.S. 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 truncated 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.

4. REGULATORY BACKGROUND

4.1 FIBRINOGEN

Fibrinogen for intravenous use was marketed in the U.S. by several companies in the twentieth century. It was used to treat not only congenital fibrinogen deficiency, but was also used to treat obstetric (postpartum) bleeding. The FDA revoked all licenses for fibrinogen concentrates in 1977 because of the risk of hepatitis transmission and insufficient evidence 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 tradenames “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 Haemocompletan® P, except that the cryoprecipitate and the albumin solution, used as stabilizer, are from plasma collected at U.S. licensed facilities.

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 rare plasma protein disorders. 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 (see APPENDIX 1) The pivotal Phase 3 study for the BLA, Study No. B13023_2001, uses maximum clot firmness (MCF), as determined by thromboelastometry (APPENDICES 2, 3), 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.

Fibrinogen is currently licensed in 7 European countries under the tradename Haemocompletan® P. For the US market, RIASTAP™ will be used as the trade name. RIASTAP™ was granted Orphan Drug Designation by the FDA for "treatment of fibrinogen deficient patients" on 13 March 2008.

4.2 RIASTAP™: REGULATORY CHRONOLOGY OF THE BLA

There are no U.S. licensed Fibrinogen concentrates at the present time.

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 RIASTAP for 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 13023_2001) and MCF as measured by thromboelastometry as a surrogate endpoint, together with previous clinical studies, post-marketing surveillance data from Europe, 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. The surrogate endpoint will then be validated by showing an association between MCF and clinical efficacy in a post-marketing study.
- November 2006: IND submitted (BB-IND (b)(4)) with the PK and evaluation of MCF as a surrogate endpoint for hemostatic efficacy.
- January 2007: CBER notified CSL Behring that the study may proceed.
- July 2007: The post-marketing protocol (study 13023_3001) to validate the surrogate endpoint was submitted to CBER
- March 2008: Orphan drug status granted
- July 17 2008: BLA submitted

5.0 BASIS FOR LICENSURE

The applicant conducted a pivotal study B13023_2001 as a prospective, open, uncontrolled trial in 15 subjects to collect PK and safety data and demonstrate hemostatic efficacy using MCF, as determined by thromboelastometry, as a surrogate endpoint. The duration of the

study was about 12 months. A retrospective physician survey (Survey CE1221_1) was conducted and provided data from 31 physicians regarding 100 patients that will be used as the historical control for a post-marketing study. Study No. B13023_3001 is a post-marketing commitment study (prospective, open, historically controlled Phase 4 study in 23 evaluable subjects) to validate a correlation between MCF the surrogate efficacy endpoint used in Study B13023_2001, and clinical efficacy of stopping acute bleeding.

RIASTAP™ was found to be effective in increasing clot firmness in patients with congenital fibrinogen deficiency (afibrinogenemia) as measured by thromboelastometry. After administration of RIASTAP™, fibrinogen levels increased to the desired plasma level. The median *in vivo* recovery indicated that a dose of 70 mg/kg fibrinogen increases fibrinogen plasma concentration by approximately 120 mg/dL and exceeds the minimal hemostatic level of 100 mg/dL (normal range 200-450 mg/dL). The safety profile appears to be acceptable.

5.1 SYNOPSIS OF PROTOCOL FOR STUDY B13023_2001, PIVOTAL STUDY

Study B13023_2001 was conducted as a multinational, prospective, open-label, uncontrolled study. Each subject received a single intravenous infusion of 70 mg/kg of RIASTAP™. 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 objective of the study were to compare 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 h after administration of 70 mg/kg of the product is higher and correlates with expected plasma fibrinogen levels compared to baseline and to determine the single-dose pharmacokinetics of RIASTAP™ in subjects with congenital fibrinogen deficiency.

A separate objective was to assess the safety of RIASTAP™ in subjects with congenital fibrinogen deficiency especially with regards to thrombogenicity.

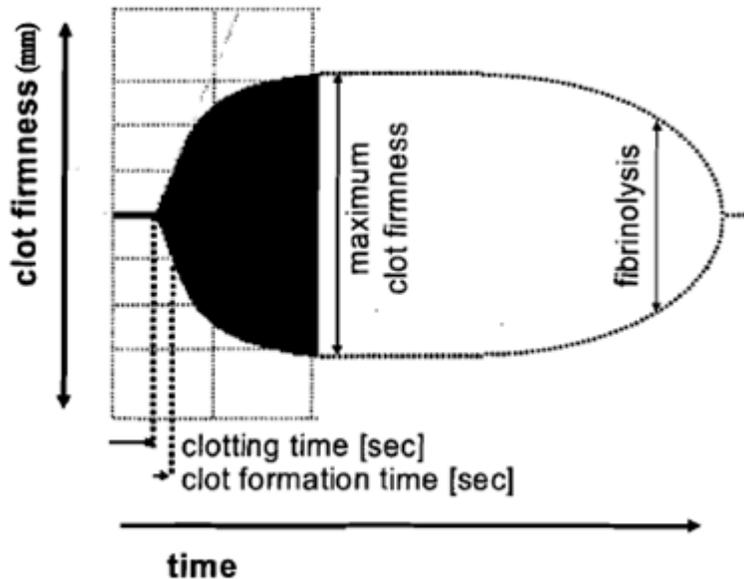
The primary surrogate endpoint of the study was the difference between the pre-infusion (i.e. just before infusion of RIASTAP™) and 1 h post-infusion MCF (or maximal amplitude of the clot, MA, in mm). The statistical null hypothesis ($H_0: \Delta = 0$) of no difference was tested against two sided alternative hypothesis ($H_1: \Delta \neq 0$) with a one sample t-test for paired observations. The maximum permitted type 1 error was 5%, two sided.

The efficacy variable measured in this study was the surrogate endpoint MCF, a functional parameter which depends on the activation of platelets and coagulation, including the fibrinogen content of the plasma sample and the polymerization/crosslinking of the fibrin

network. Platelet activity was abolished (see below) in order to assess the fibrinogen contribution to clot firmness. In order to avoid site variability, 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..

Rationale for using MCF as determined by thromboelastometry as a surrogate endpoint

In the literature thromboelastometry 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 thromboelastometry 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 (APPENDICES 2, 3).



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.

To evaluate MCF as the surrogate endpoint for efficacy and to show a direct correlation of MCF to fibrinogen levels, CSL Behring performed an *in vitro* study to validate MCF as measured by thromboelastometry as a functional assay for fibrinogen (Kalina U; Blood Cog fibr). Clotting time and MCF were determined in: a normal human plasma pool, a fibrinogen deficient plasma pool, normal whole blood, and individual plasma samples from 17 subjects with fibrinogen deficiency using their validated methods. Plasma samples spiked with varying concentrations of exogenous fibrinogen were also measured. Results were compared with the Clauss assay 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 showed

a linear correlation with both the functional Clauss assay ($r^2 = 0.93$) and the antigen binding ELISA ($r^2 = 0.95$) (see APPENDIX 3).

In order to assess only the fibrinogen effect, the platelet contribution to MCF was abolished by cytochalasin D. In unspiked plasma samples from individual subjects with fibrinogen deficiency, fibrinogen was undetectable by thromboelastometry. In plasma of fibrinogen-deficient individuals, a dose–response relationship was demonstrable in MCF as a function of added exogenous fibrinogen. The MCF values correlated well with the other assays performed (Clauss, ELISA).

For the pivotal study, 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 (subjects with missing MCF values were not included).

Safety Monitoring

Safety assessments included adverse events (AEs), physical examinations and vital signs, laboratory assessments (hematology, biochemistry, and thrombogenicity), and viral monitoring including testing for HIV-1 and 2, HAV, HBV, HCV, and B19 virus. Viral serology was checked at baseline using an enzyme immunoassay 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, and at day 30 and 90 for HIV, HBV and HCV.

Results of pivotal study B13023_2001

Pharmacokinetics

A prospective, open-label, uncontrolled, multicenter pharmacokinetic study of RIASTAP™ was conducted in 5 females and 9 males with congenital fibrinogen deficiency, ranging in age from 8 to 61 years, 2 children (8 and 11 years], 3 adolescents (12, 14 and 16 years), and 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 (one patient was not analyzed for PK because samples were not drawn adequately). The fibrinogen activity was determined by the Clauss assay (functional assay) and antigen levels were determined by a fibrinogen specific ELISA method. The pharmacokinetic parameters of RIASTAP™ in patients with congenital fibrinogen deficiency are summarized in the following Table.

Pharmacokinetic Parameters (n =14) of RIASTAP

Parameters	Mean ± SD
Half-life [hours]	78.7 ± 18.1 (55.7-117.2)
C _{max} [g/L]	1.4 ± 0.27 (1.00-2.10)
AUC for dose of 70 mg/kg [mg*hr/ML]	124.3 ± 24.1 (81.7-156.4)
Clearance [mL/h/kg]	0.59 ± 0.13 (0.45-0.86)
Mean residence time [hours]	92.8 ± 20.1 (66.1-126.4)
Volume of distribution at steady state [mL/kg]	52.7 ± 7.5 (36.2-67.7)

The values in parenthesis are ranges

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 ± 8.5h) and faster clearance (0.7 ± 0.1 mg/L) 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 1.3 – 2.73 mg/dL) and the mean was 1.8 mg/dL increase per mg/kg. The PK analysis using fibrinogen antigen data were concordant with those for fibrinogen activity.

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. The median *in vivo* recovery indicated that an average dose of 70 mg/kg fibrinogen increases patients fibrinogen plasma concentration by approximately 120 mg/dl which exceeds the minimal hemostatic level of 100mg/dL (normal range 200-450 mg/dL).

Safety and Efficacy

15 subjects enrolled in the sites in U.S. and Italy received RIASTAP™. 86.7% of the subjects enrolled were 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 and verified by FDA):

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.

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 statistically significant difference between the two age groups in the mean change from pre-infusion to 1h post infusion.

There were four treatment-emergent AEs (TEAEs) (epistaxis, gastroesophageal reflux disease, headache, and pain) reported by two 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 and was considered a temporally associated with RIASTAP 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, fibrinopeptide A and B were not clinically relevant. There were no reports of viral seroconversion in any patient.

The 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 mean change in MCF values closely approximated the levels expected from adding known amounts of fibrinogen to plasma *in vitro* and the observed fibrinogen levels found *in vivo* as part of the PK studies. 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.

The PK results obtained in 14 subjects (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 7MN-101FM and literature reports.

The safety profile appears to be acceptable.

5.2 STUDY B13023_3001 PHASE 4 FOR VALIDATION OF THE SURROGATE ENDPOINT

This study has been initiated as a multinational, multicenter, prospective, open, historically controlled, non-inferiority post-marketing study.

The primary objectives and endpoints of the study are:

1. To demonstrate the efficacy of RIASTAP™, by adequately controlling acute bleeding (spontaneous or after trauma) compared to the hemostatic efficacy data in the historical control on cryoprecipitate treatment obtained from a retrospective survey (Survey CE1221_1). 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 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 of MCF that was used as a surrogate endpoint for hemostatic efficacy, and was determined via thromboelastometry in the pivotal pharmacokinetic study B13023_2001. MCF will be determined prior to and 60 minutes after the end of the first infusion. In this study the correlation between clinical hemostatic efficacy and MCF will be investigated as a co-primary endpoint.
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.

5.3 SUPPORTIVE STUDIES FOR EFFICACY AND SAFETY

5.3.1 STUDY CE1221_1: CLINICAL SURVEY STUDY (HISTORICAL CONTROL FOR U.S. PHASE 4)

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.

The content of the survey was reviewed and accepted by the Agency. The survey consisted of questionnaire consisting of a general part and a patient-specific part. In the general part the following data were collected: 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. In the patient-specific part data on physicians recorded specific information on demographics, schedule and type of treatment and details of each event, were recorded.

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 U.S. was primarily on use of cryoprecipitate as fibrinogen concentrate is not licensed in the U.S.). In one center use of fresh frozen plasma, coagulation Factors VIIa and VIII concentrates was reported. Of the 100 subjects only 39 received treatment with cryoprecipitate for \geq one bleeding episode with hemostatic efficacy rating data available. The remaining 61 patients received Hemocomplettan P.

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 were on routine prophylactic treatment. A total of 517 events (483 under on demand and 34 under routine prophylaxis treatment) were recorded. For on-demand treatment the duration of treatment ranged from 4-14 days. The hemostatic efficacy rating was comparable between cryoprecipitate and Hemocomplettan P: 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 most commonly used test to assess fibrinogen levels was the Clauss assay, a functional test.

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).

In conclusion, based on the physicians' assessment of efficacy, it appeared that both treatments (cryoprecipitate and Hemocomplettan P) were equally effective. Two patients on prophylaxis had a thrombotic event, one received cryoprecipitae and one received Hemocomplettan P. .

5.3.2 PHASE 1 PK STUDY (CONDUCTED IN EUROPE)

This study was conducted as a phase 1, multicenter, multinational, uncontrolled to assess PK and safety of Hemocomplettan P. PK was assessed in 6 subjects with congenital

fibrinogen deficiency after infusion of 70 mg/kg of Hemocomplettan P. The median *in vivo* recovery was 1.45mg/dL (1.36-1.91). Six AEs were reported and included infusion site pain, headache and dizziness and elevated temperature, dizziness and pallor. All the AEs were considered to be non-serious and needed no intervention.

5.3.3 STUDY 7MN-501FM

This was a multicenter Phase 4 study conducted in Europe 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 (n = 12) 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); 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 hypermenorrhoea, 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 mean 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.

5.4 SUPPORTIVE STUDIES TO SUPPORT SAFETY

Safety data are available from the pivotal study B13023_2001 and from post-marketing experience in Europe since 1986.

- An open-label, uncontrolled, prospective Phase 1 study in Europe (Study 7MN-101FM) was conducted between April to November 1993.
- A retrospective Phase 4 study in Europe (Study 7MN-501FM) was conducted between May 1985 and February 1992.

- Additional virus safety data are available from an earlier study conducted in subjects with congenital fibrinogen deficiency in Europe (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. This study was not designed to collect safety information.

In the five clinical studies, a total of 39 patients were monitored for safety.

5.4.1 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, fibrinopeptideA and B are not clinically relevant. There were no reports of viral seroconversion in any patients.

5.4.2 STUDY 7MN-101FM

Six subjects were enrolled in the study. Six AEs were observed in four 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

In subject (b)(6) the investigator classified the event as allergic reaction. All the (b)(6) were considered to be non-serious and needed no intervention.

5.4.3 STUDY 7MN-501FM

Twelve 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.

One 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.

5.4.4 STUDY 7D-402XX-RS

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

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

5.5 POST-MARKETING ADVERSE EVENT DATA IN EUROPE: PASSIVE REPORTING

CSL Behring has received a total of 45 adverse event reports for Hemocomplettan P since it began marketing in Europe (1986-2008), corresponding to one report for every 3,414 doses distributed over this time period. The table presented is the sponsor’s assessment of the adverse reports. Because post-marketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or to establish a causal relationship to product exposure (APPENDIX 6).

Overview of ADRs reported 1986-2008:

Adverse Drug Reaction	Number of Reported Cases	Number and Causality of Reported Cases
Allergic-allergoid/anaphylactic-anaphylactoid reaction (including generalized reactions such as chills, fever, nausea, vomiting)	19	16 possibly related, 3 insufficient data
Thromboembolic events	9	8 possibly related, 1 insufficient data
Suspected transmission of infectious disease	14	13 unrelated, 1 insufficient data
Lack of effect ^a	3	2 insufficient data, 1 unrelated

6. CONCLUSIONS

6.1 EFFICACY

Overall, FDA concludes that when patients with congenital fibrinogenemia are given 70 mg/kg of RIASTAP, the expected *in vivo* recovery and half-life is observed when compared to the literature and other studies conducted with the product. MCF, the surrogate efficacy parameter, was increased in congenital deficient patients after RIASTAP administration, to levels that correlated well with expected fibrinogen levels. The clinical significance, i.e. correlation with hemostatic efficacy, will be evaluated in Phase 4 post-marketing study.

6.2 SAFETY

The safety profile appears to be acceptable. However, additional safety with regards to thromboembolism will be evaluated in the Phase 4 study.

6.2.1 THROMBOGENICITY:

The potential risk of thrombogenicity exists due to the pharmacological effect of the product. Careful monitoring of fibrinogen levels is needed throughout the therapeutic treatment period. The aim is to maintain target peak levels at 100 mg/dL with an accepted lower limit of 80 mg/dL for minor and 150 mg/dL for major events.

6.3 CONCLUSIONS

These results are sufficient for approval under the Accelerated Approval pathway. However, a Phase 4 study is required to determine whether the surrogate marker, MCF, correlates with clinical efficacy, i.e. hemostasis.

7. QUESTIONS TO THE COMMITTEE

Question #1

With regard to safety and efficacy:

- a) Is the safety profile acceptable?
- b) Did the study show that MCF increase was significant and likely to be clinically meaningful?

Question#2

Is the phase 4 study adequately designed to determine whether the surrogate endpoint correlates with a meaningful clinical endpoint?

APPENDIX 1

ACCELERATED APPROVAL

In the *Federal Register* of December 11, 1992 (57 FR 58942), FDA published final regulations under which the Agency would accelerate the approval of certain new drugs and biological products for serious or life-threatening illnesses.

21 CFR 601.41 states: “FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefits or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.”

Accelerating Availability of New Drugs for Patients with Serious Diseases

Speeding the development and availability of drugs that treat serious diseases are in everyone's interest, especially when the drugs are the first available treatment or have advantages over existing treatments. The Food and Drug Administration (FDA) has developed three distinct and successful approaches to making such drugs available as rapidly as possible: *Priority Review*, *Accelerated Approval*, and *Fast Track*. Because each of these approaches implies speed, there can be confusion about the specific meaning of each and the distinctions among them.

Accelerated Approval

When studying a new drug, it can take a long time - sometimes many years - to learn whether a drug actually provides real improvement for patients – such as living longer or feeling better. This real improvement is known as a “clinical outcome.” Mindful of the fact that obtaining data on clinical outcomes can take a long time, in 1992 FDA instituted the *Accelerated Approval* regulation, allowing earlier approval of drugs to treat serious diseases, and that fill an unmet medical need based on a surrogate endpoint.

A surrogate endpoint is a marker - a laboratory measurement, or physical sign - that is used in clinical trials as an indirect or substitute measurement that represents a clinically meaningful outcome, such as survival or symptom improvement. The use of a surrogate endpoint can considerably shorten the time required prior to receiving FDA approval.

Approval of a drug based on such endpoints is given on the condition that post marketing clinical trials verify the anticipated clinical benefit.

The FDA bases its decision on whether to accept the proposed surrogate endpoint on the scientific support for that endpoint. The studies that demonstrate the effect of the drug on the surrogate endpoint must be “adequate and well controlled” studies, the only basis under law, for a finding that a drug is effective.

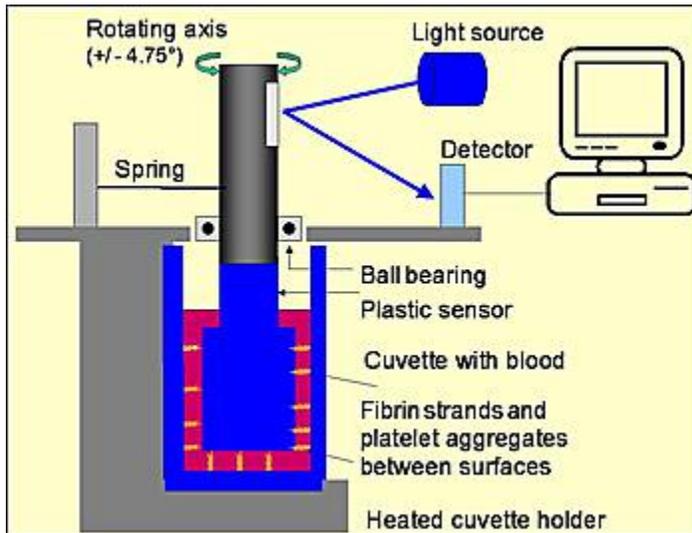
Use of a surrogate can save valuable time in the drug approval process. For example, instead of having to wait to learn if a drug actually can extend the survival of cancer patients, the FDA might now approve a drug based on evidence that the drug shrinks tumors because tumor shrinkage is considered *reasonably likely to predict* a real clinical benefit. In this example, an approval based upon tumor shrinkage can occur far sooner than waiting to learn whether patients actually lived longer. The drug company will still need to conduct studies to confirm that tumor shrinkage actually does predict that patients will live longer. These studies are known as phase 4 confirmatory trials.

If the confirmatory trial shows that the drug actually provides a clinical benefit, then the FDA grants traditional approval for the drug. If the confirmatory trial does not show that the drug provides clinical benefit for patients, FDA has regulatory procedures in place that could lead to removing the drug from the market.

APPENDIX 2

Thromboelastometry

ROTEM® stands for rotation thromboelastometry and is an enhancement of classical thromboelastography, a powerful technique for the assessment of blood coagulation disorders.



Principle

Blood is added into a disposable cuvette in a heated cuvette holder
 The disposable pin (sensor) is fixed on the tip of a rotating axis
 The axis is guided by high precision ball bearing system
 The axis rotates back and forth
 The axis is connected with a spring for measurement of elasticity.

The exact position of the axis is detected by reflection of light on a small mirror on the axis.

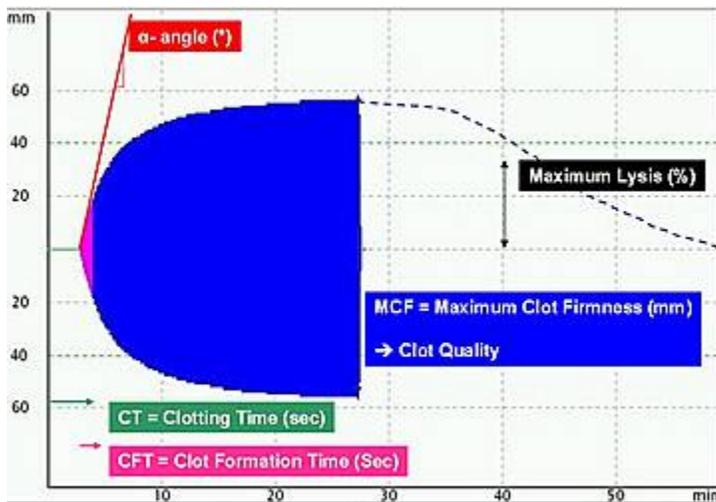
The data obtained are then analysed by a computer

The loss of the elasticity when the sample clots leads to a change in the rotation of the axis. The data obtained are then visualized as a thromboelastogram.

Results

While clotting assays detect **when** blood clots, thromboelastometry (TEM) informs on **how** blood clots and **if the clot is, and remains stable**.

Typical reaction curves



Numerical data

ROTEM® Parameter	Definition	Information
Clotting time CT (sec)	time from start of measurement until the start of clot formation	initiation of clotting, thrombin formation, start of clot polymerisation
Clot formation time CFT (sec)	time from the begin of clot formation until an amplitude of 20 mm is reached	fibrin polymerisation, stabilisation of the clot with thrombocytes and F XIII
Maximum clot firmness MCF (mm)	clot stability and firmness	increasing stabilisation of the clot by the polymerised fibrin, thrombocytes as well as F XIII
Maximum lysis ML (% of MCF)	reduction of the clot firmness after MCF in relation to MCF	stability of the clot (ML < 15%) or fibrinolysis (ML > 15% within 1h)

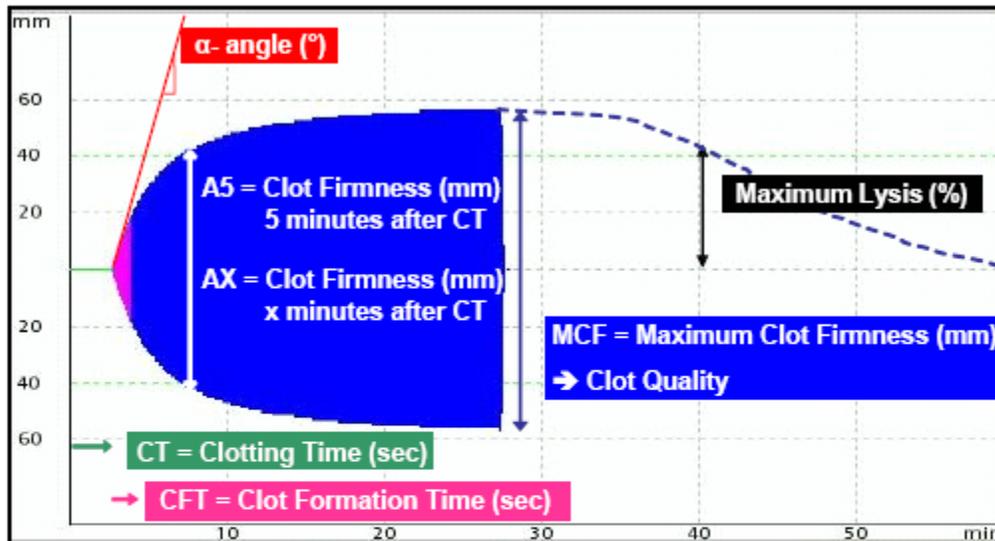
The different parameters in thromboelastometry (TEM) are dependent on:

- the activity of the plasma coagulation system (including fibrinogen)
- platelet function

fibrinolysis
 many factors which influence these interactions
 including several drugs.

TEM Interpretation

ROTEM® parameters



CT (clotting time): time from start of measurement until initiation of clotting
 => initiation of clotting, thrombin formation, start of clot polymerisation

CFT (clot formation time): time from initiation of clotting until a clot firmness of 20mm is detected
 => fibrin polymerisation, stabilisation of the clot with thrombocytes and F XIII

MCF (maximum clot firmness): firmness of the clot
 => increasing stabilisation of the clot by the polymerised fibrin, thrombocytes as well as F XIII

ML (maximum lysis): reduction of the clot firmness after MCF in relation to MCF
 => stability of the clot (ML < 15%) or fibrinolysis (ML > 15% within 1h)

ROTEM® Reference values

test name (reagent)	CT (s)	CFT (s)	α Angle	A10(mm)	A15(mm)	A20(mm)	A25(mm)	MCF(mm)	CLI 30(%)	ML (%) ²
INTEM	100-240	30-110	70-83	44-66	48-69	50-71	50-72	50-72	94-100	< 15
HEPTEM	Comparison with INTEM. A better clot quality in HEPTEM as compared to INTEM indicates the presence of heparin or heparin-like anticoagulants in the sample.									
EXTEM	38-79	34-159	63-83	43-65	48-69	50-71	50-72	50-72	94-100	< 15
APTEM	Comparison with EXTEM. A better clot formation with ap-TEM® or APTEG-S when compared to ex-TEM® is an early sign of hyperfibrinolysis.									
FIBTEM	n.d	n.d	n.d	7-23	n.d	8-24	n.d	9-25	n.d	n.d
	MCF < 9 mm is a sign of decreased fibrinogen or disturbed clot polymerisation. MCF > 25 mm is a sign of elevated fibrinogen levels (which may lead to a normal EXTEM or INTEM in spite of thrombocytopenia).									
NATEM	300-1000 ¹⁾	150-700 ¹⁾	30-70 ¹⁾			35-60 ¹⁾		40-65 ¹⁾	94-100 ¹⁾	< 15 ¹⁾

Referenz: Lang T, Bauters A, Braun SL, Poetzsch B, von Pape K-W, Kolde H-J, Lakner M. Multi-centre investigation on reference ranges for ROTEM® thromboelastometry (eingereicht in Blood Coagulation and fibrinolysis)

Test specificities: EXTEM & INTEM

EXTEM:

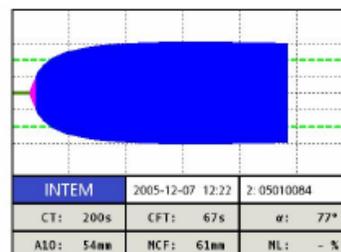
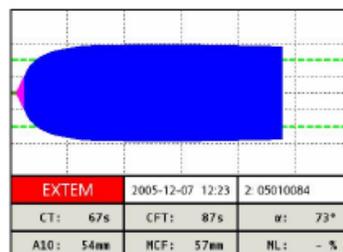
- extrinsic screening test
- CT not sensitive for heparin (up to 4 U/ml UFH in blood)

INTEM:

- intrinsic screening test
- CT sensitive for heparin (UFH)
- CT prolongation from > 0,15 U/ml UFH in blood

EXTEM & INTEM amplitude and CFT influenced by:

- fibrinogen
- platelets



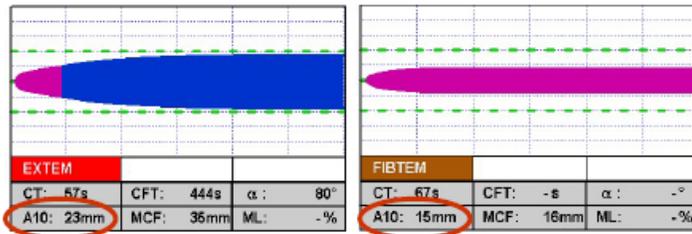
Test specificities: FIBTEM

FIBTEM:

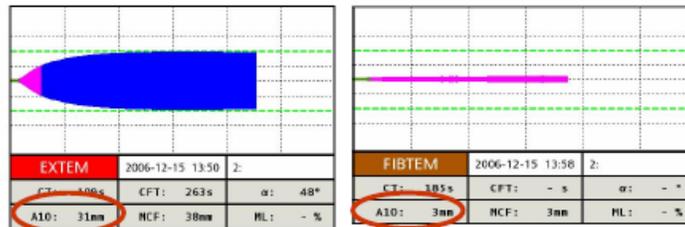
- activation as in EXTEM
- platelet inhibition reagent added

→ TEMogram shows isolated fibrinogen contribution to Clot firmness

- A) • **EXTEM:** amplitude low
 • **FIBTEM:** amplitude normal
 => fibrinogen level OK
 => platelet deficiency



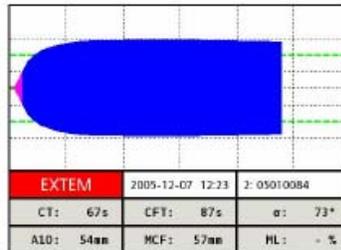
- B) • **EXTEM:** amplitude low
 • **FIBTEM:** amplitude low
 => fibrinogen deficiency



Normal haemostasis with different tests

EXTEM & INTEM

- Normal CT
- Normal amplitudes
- No hyperfibrinolysis visible



- FIBTEM:** Amplitude normal
 => fibrinogen level sufficient

&

- EXTEM:** Amplitude normal



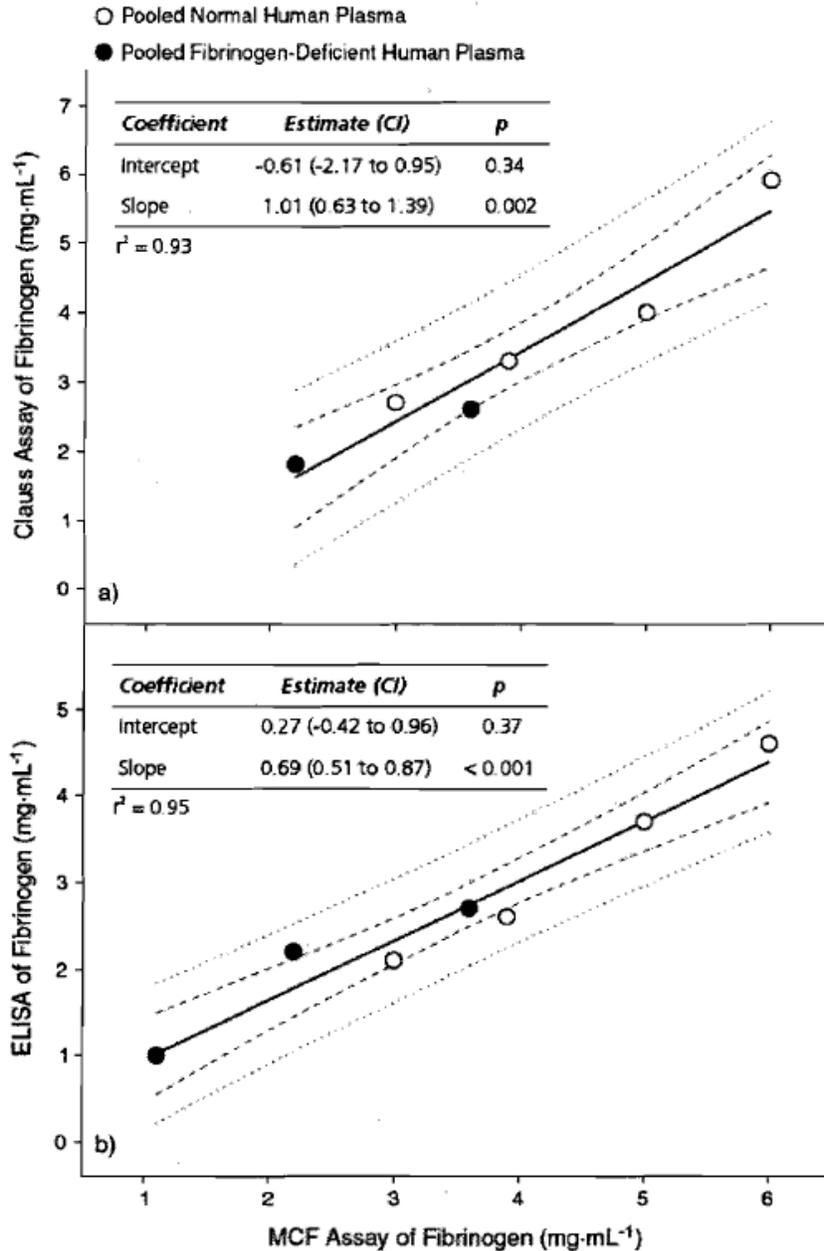
- => platelets normal

APTEM ≈ EXTEM

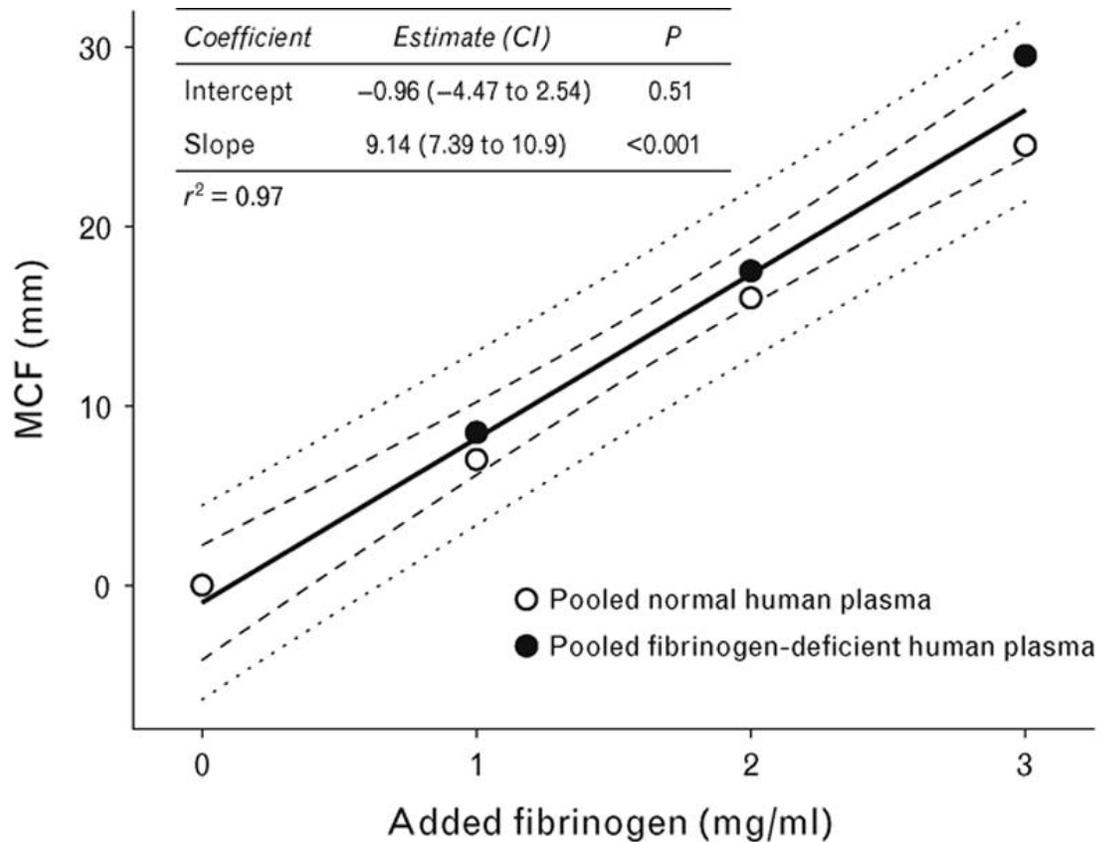
- => No hyperfibrinolysis

APPENDIX 3
Kalina, Uwe et al

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 of maximum clot firmness determinations ($n = 7$) following addition of 0, 1, 2 or 3 mg/ml exogenous fibrinogen to normal human plasma pool (open circles) or fibrinogen-deficient human plasma pool (closed circles). Maximum clot firmness without added fibrinogen was subtracted from values of pooled normal human plasma. Dashed lines indicate confidence interval of the regression and dotted lines indicate confidence interval for prediction of new sample values. CI, 95% confidence interval; MCF, maximum clot firmness.

APPENDIX 4

Fibrinogen Assay (Clauss Technique)²⁴

Principle

Diluted plasma is clotted with a strong thrombin solution; the plasma must be diluted to give a low level of any inhibitors (e.g., FDPs and heparin). A strong thrombin solution must be used so that the clotting time over a wide range is independent of the thrombin concentration.

Reagents

Calibration plasma. With a known level of fibrinogen calibrated against an International Reference Standard.

Make dilutions of the calibration plasma in veronal buffer to give a range of fibrinogen concentrations (i.e., 1 in 5, 1 in 10, 1 in 20, and 1 in 40). Part (0.2 ml) of each dilution is warmed to 37°C, 0.1 ml of thrombin solution is added, and the clotting time is measured. Each test should be performed in duplicate. Plot the clotting time in seconds against the fibrinogen concentration in g/l on log/log graph paper. The 1 in 10 concentration is considered to be 100%, and there should be a straight line connection between clotting times of 5 and 50 sec. Make a 1 in 10 dilution of each patient's sample and clot 0.2 ml of the dilution with 0.1 ml of thrombin.

The fibrinogen level can be read directly off the graph if the clotting time is between 5 and 50 sec. However, outside this time range a different assay dilution and mathematic correction of the result will be required (i.e., if the fibrinogen level is low and a 1 in 5 dilution is required, divide answer by 2 and for a 1 in 20 dilution multiply answer by 2).

The clot formed in this method may be "wispy" as a result of the plasma being diluted, and end-point detection may be easier with optical or mechanical automated equipment. These have been assessed with available substrates and give reasonably consistent results.²⁵ The high concentration of thrombin used raises the risk of carry over into subsequent tests.

Normal Range

The normal range is 1.8–3.6 g/l.

Interpretation

The Clauss fibrinogen assay is usually low in inherited dysfibrinogenaemia but is insensitive to heparin unless the level is very high (>0.8 u/ml). High levels of FDPs, >190 µg/ml, may also interfere with the assay.²⁶ Because the chrometric Clauss assay is a functional assay it will generally give a relevant indication of fibrinogen function in plasma. When an inherited disorder of fibrinogen is suspected, a physicochemical estimation should be obtained (e.g., clot weight estimate of fibrinogen or total clottable fibrinogen or an immunological measure; see page 398). If a dysfibrinogenaemia is present, it will reveal a discrepancy between the (functional) Clauss assay and the physical amount of fibrinogen present.

APPENDIX 5

Cumulative (Log₁₀) Virus Inactivation/Reduction in RIASTAP™

Manufacturing Step	Virus Reduction Factor (log ₁₀)						
	Enveloped viruses				Non-enveloped viruses		
	HIV	BVDV	WNV	HSV-1	HAV	CPV	B19V
Cryoprecipitation	n.d.	n.d.	n.d.	1.6*			n.d.
Al(OH) ₃ adsorption/ glycine precipitation/ Al(OH) ₃ adsorption	2.8	1.5	n.d.	(0.9) [†]	2.4	2.8	n.d.
Pasteurization	≥ 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 (log₁₀)	≥ 12.4	≥ 12.7	N/A	≥ 10.7	≥ 7.7	6.0	N/A

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

* PRV – as HSV-1 a herpes virus – is reduced by cryoprecipitation by 1.6 log₁₀

[†] Not included in the calculation of the cumulative virus reduction factor.

n.d., not done

APPENDIX 6
Safety Data as verified by FDA

Non serious AEs in clinical trials

Occurrence of AE	Study B13023_2001 (N=15; 15 doses)	Study 7MN-101FM (N=6; 6 doses)	Study 7MN-501FM (N=12; 151 doses)	Study 7D-402XX-RS (N=6^a; 72 doses)
Subjects with ≥ 1 AE	2	4	0	0
<i>Subjects with ≥ 1 possibly treatment-related AE</i>	1	2	NA ^b	0

AE = adverse event;

^a Four subjects analyzed in original study report; 2 subjects added to analysis by report amendment.

^b No information available on casual relation of AE to study drug in clinical study report.

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

Case No.	Age (yrs)	Indication for treatment	Time between HFC Dose and Event	Lab Event (year)	Co-suspect Plasma/Blood Products/Events
V1	40	CD dysfib	9 yrs. from 1 st dose	Anti-HCV+ (1995)	Non-virus inactivated products
V2	61	AD, cardiac surgery	10 mos. from dosing	Anti-HCV+ (1995)	Plasma, PRBCs
V3	NA	AD, gynecologic surgery	Hep C dx immediately after surgery	Anti-HCV+ (1988)	No baseline test done
V4	68	AD, hemorrhagic shock	5 yrs. from dosing	HBsAg+ and HBcAg+ (1996)	5 U plasma, 14 U PRBCs
V5	NA	AD, chemotherapy	NA	HCV+ (1994)	PRBCs, platelets
V6	40	AD, heart surgery	NA (treated in 1996)	HCV+ (NA)	Platelets
V7	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
V8	71	AD, hip surgery	21 mos. from dosing	HCV+ (1997)	PRBCs, PCC for massive intraoperative bleeding

V9	10	AD, chemotherapy for ALL	26 mos. from last dose in 04/94	HCV+ (06/96) (<i>HCV neg</i> <i>in 05/96</i>)	PRBCs, platelets
V10	NA	AD, surgery	Reported 14 yrs. from dosing	HCV+ (NA)	Plasma, patient was a nurse
V11	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
V12	49	NA	NA	HCV+ (NA)	Multiple other blood products
V13	NA	CD	NA	HCV+ (NA)	Plasma
V14	44	AD, DIC/multiple trauma	25 to 37 mos. from single dose on 11/01	HCV+ (2004)	PRBCs, platelets, ATIII

Post marketing thromboembolic events in Europe (1986-2008)

Age (yrs)	Indication for Treatment	Major Symptoms/ Underlying Conditions (Comment)	Dosing of Fibrinogen concentrate	Time between Last Fibrinogen Dose and Event	Event ^a	Co-suspect Products
15 days	AD, pulmonary bleeding after cardiac surgery	Congenital heart defect	2 g total dose	7 days	Thrombosis of SC arteries and truncus brachio-cephalicus	Activated FVII, activated PCC
44	CD afib	<i>(possible antibody interference with heparin)</i>	Prophylactic dosing for 21 yrs (4 g/wk)	NA	Recurrent occlusion of anterior tibial artery	Recurred despite heparin, lepirudin therapy
23	CD afib	-	1 g total dose	NA	Multiple arterial thromboses	4.5 g of another fibrinogen concentrate
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	
32	CD afib	-	On-demand tx for massive hemorrhage after iatrogenic arterial injury (8-g single doses)	NA	Massive proximal DVT/ successfully treated	-
18	CD afib	Implanted infusaport	Prophylactic dosing for many yrs; dose increased for surgical procedure	15 days post-op	SC/jugular thrombosis	-
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	-

Case No.	Age (yrs)	Indication for Treatment	Major Symptoms/Underlying Conditions (<i>Comment</i>)	Dosing of HFC	Time between Last HFC Dose and Event	Event ^a	Co-suspect Products
TE1	15 days	AD, pulmonary bleeding after cardiac surgery	Congenital heart defect	2 g total dose	7 days	Thrombosis of SC arteries and truncus brachiocephalicus	Activated FVII, activated PCC
TE2	44	CD afib	<i>(possible antibody interference with heparin)</i>	Prophylactic dosing for 21 yrs (4 g/wk)	NA	Recurrent occlusion of anterior tibial artery	Recurred despite heparin, lepirudin therapy
TE3	23	CD afib	-	1 g total dose	NA	Multiple arterial thrombosis	4.5 g of another fibrinogen concentrate
TE4	41	CD afib	-	Dosed for 2 yrs (2 g every 7-14 days)	3 days	Central retinal vein thrombosis	-
TE5	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	-
TE6	32	CD afib	-	On-demand tx for massive hemorrhage	NA	Massive proximal	-

				after iatrogenic arterial injury (8-g single doses)		DVT/ successfully treated	
TE7	18	CD afib	Implanted infusaport	Prophylactic dosing for many yrs; dose increased for surgical procedure	15 days post-op	SC/jugular thrombosis	-
TE8	69	CD hypfib	Hematoma and hemorrhage/ AML	Not reported	48 hrs	Micro- vascular thrombosis	Aprotinin (i.v. and infusion)
TE9	32	CD afib	-	On-demand tx for large SDH (2 g every other day for 3 wk)	3 wks	Pulmonary embolus/ recovered	-