BLOOD PRODUCTS ADVISORY COMMITTEE

HUMAN FIBRINOGEN CONCENTRATE (RIASTAP™) BRIEFING DOCUMENT

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Biotherapies for Life™

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EXECUTIVE SUMMARY

This Briefing Package summarizes the Biologics License Application (BLA) for human fibrinogen concentrate (HFC), proposed trade name Riastap™, for the treatment of congenital fibrinogen deficiency. HFC is manufactured by CSL Behring GmbH in Marburg, Germany, from US-sourced human plasma.

The prevalence of congenital fibrinogen deficiency in the general population is estimated to be approximately 1 per million [Mannucci 2004; de Moerloose 2008]; therefore, the estimated prevalence in the United States is approximately 300 patients. There are 3 types of congenital fibrinogen deficiencies: afibrinogenemia, characterized by the absence of plasma fibrinogen; hypofibrinogenemia, in which plasma fibrinogen levels are significantly below normal; and dysfibrinogenemia, in which fibrinogen antigen levels are normal but fibrinogen function is markedly impaired due to one or more genetic mutations. The combination of both low fibrinogen levels and impaired fibrinogen function, known as hypodysfibrinogenemia, is occasionally observed.

Fibrinogen is an essential component of the coagulation cascade, a physiologic substrate of 3 enzymes: thrombin, factor XIIIa, and plasmin. Its principal role results from its conversion into insoluble fibrin clots by the action of thrombin. Defects in fibrinogen function can be associated with an increased risk for both hemorrhagic and thrombotic disorders.

In the United States, currently available treatments for congenital fibrinogen deficiency are infusions of cryoprecipitate or of fresh-frozen or otherwise prepared plasma. There are several limitations to these therapies, the most important being the large volume of unwanted and unnecessary proteins that may increase the risk of allergic and anaphylactic reactions, as well as transfusion-related acute lung injury (TRALI). The absence of viral inactivation procedures in the manufacturing process, along with time constraints for preparation, inventory, and volume, pose further disadvantages for the currently available therapies in the United States.

The Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) has emphasized the importance of virally safe blood factor concentrates and, for this reason, has discouraged the use of cryoprecipitate for the treatment of von Willebrand disease and hemophilia. That recommendation also extends to encouraging blood-plasma manufacturers to produce factor concentrate therapies for rare disorders. Specifically, in Document #182, *MASAC Recommendations Concerning the Treatment of Hemophilia and Other Bleeding Disorders (revised April 2008),* the NHF and MASAC recommend that plasma manufacturers take the necessary steps to ensure the continued availability of plasma-derived clotting factor concentrates for individuals with rare bleeding disorders. Supporting reasons include the following:

- Such concentrates are safer than the alternatives of plasma and cryoprecipitate, which are not virally attenuated.
- Such concentrates provide the ability to raise clotting factor levels to a desired target level without the risk of volume overload, which is another drawback of plasma.
- Such concentrates allow for prophylactic treatment, if indicated by severity of the disease and frequency of bleeding episodes.

Consisting of physiologic human fibrinogen, HFC was originally licensed for marketing in Germany and Austria in 1986 under the name Haemocomplettan® P. It is now also marketed in 10 other countries and is available under the Special Access Program in Canada. A retrospective, international survey of physicians treating congenital fibrinogen deficiency (Study 1221) conducted by CSL Behring indicated that, outside the United States and Canada, fibrinogen concentrate is the preferred mode of therapy. Currently, 4 fibrinogen concentrates are commercially available outside the United States.

The projected advantages of HFC over other therapies include:

- directly targeted correction of the underlying deficiency
- no exposure to extraneous blood proteins
- reduced risk of thrombosis and virus transmission
- reduced overall volume of infusion.

The risk of thrombotic complications is anticipated to be lower with a purified fibrinogen concentrate such as HFC than with cryoprecipitate, which contains procoagulants such as factor VIII and von Willebrand factor (vWF). A strict set of protocols for plasma-donor selection and plasma-pool screening, followed by validated manufacturing processes that include pasteurization and other virus-reduction steps, ensure the purity and safety of the HFC product.

The efficacy and safety of HFC in the proposed indication of congenital fibrinogen deficiency have been demonstrated in the pivotal study (Study 2001) of 15 subjects conducted from 2007 to 2008, with maximum clot firmness (MCF) as the surrogate efficacy end point; and described in the retrospective clinical survey (Study 1221) of 100 patients conducted from 2002 to 2003; and the phase IV retrospective multicenter study (Study 501) of 12 patients conducted from 1985 to 1992.

Further clinical trial evidence of HFC safety has been gathered from pharmacokinetic (PK) Study 101 in 6 subjects, conducted in 1993; virus safety study 402 in 6 subjects, conducted from 1985 to 1987; and Clinical Observational Monitoring Project (COMP) 7D-501 in 92 patients with acquired fibrinogen deficiency, conducted from 1991 to 1994. Furthermore, there has been over 22 years of post-marketing surveillance, in which only 49 adverse drug reactions (ADRs) have been reported, reflecting distribution of approximately 1 million grams of HFC.

HFC was available for more than 15 years in Europe prior to the discussion of development for the United States, where a stricter regulatory environment precluded submission of a market application. Discussion with the Center for Biologics Evaluation and Research (CBER), Office of Blood Research and Review (OBRR) in 2002 resulted in a recommendation for the sponsor to conduct a survey of physicians treating congenital fibrinogen deficiency to gather baseline information about treatment patterns, types of bleeding, and dosing and to help to establish a historical control for subsequent post marketing commitment clinical study. This retrospective survey of physicians (Study 1221) including data from 100 patients was completed in 2003.

In June 2005, the FDA held the Biological Therapeutics for Rare Plasma Protein Disorders Public Workshop. One of the key recommendations was to encourage companies to develop innovative therapies for rare blood disorders by supporting new concepts for clinical trial designs and clinical end points, including surrogate end points to support accelerated approval. With this conceptual support, and following discussions with regulatory authorities after the workshop, CSL Behring renewed its commitment to the development of HFC for the US market.

FDA accelerated approval regulations facilitate the approval of drugs and biologics for serious or life-threatening illnesses. For biologics, the accelerated approval process is discussed in *Subpart E, 21 CFR 601.41: Approval based on a surrogate end point or on an effect on a clinical end point other than survival or irreversible morbidity.* This provision permits the approval of biological products based on a surrogate end point that is likely to predict clinical benefit. Approval is contingent on post-marketing studies to verify the product's clinical benefit. To facilitate the accelerated approval of HFC, CSL Behring and CBER agreed to a clinical development program consisting of 2 additional studies, along with the retrospective survey of physicians:

- Study 2001, a pivotal, phase II prospective, open-label PK and safety study using a surrogate end point—MCF—for hemostatic efficacy. This study has been completed.
- Study 3001, a phase IIIb post-marketing commitment study to 1) demonstrate the safety and hemostatic efficacy of HFC compared with the historical control established in the retrospective survey of physicians (Study 1221), and 2) verify the relationship between MCF and hemostatic efficacy. This study is ongoing.

In March 2008, HFC received orphan drug designation. CSL Behring submitted the BLA in July 2008; the FDA filed the BLA in August 2008 and granted priority review. Contingent approval (Subpart E, 21 CFR 601.41) of the BLA would be based on the results of Study 2001 and successful completion of Study 3001.

The pivotal PK and safety study (Study 2001) included 15 subjects, age ≥6 years, with congenital afibrinogenemia, who were treated with HFC at a median dose of 77 mg/kg body weight. MCF, the surrogate hemostatic efficacy end point, was measured pre-infusion and 1 hour post-infusion by rotational thromboelastometry (ROTEM®). MCF is a measure of the structural integrity of a clot, reflecting the underlying effectiveness of the fibrinogen present to form a fibrin clot.

The mean MCF (± SD) at 1 hour post-infusion was 10.3 ± 2.7 mm for the 13 subjects who had complete data (Note: At baseline MCF was 0 for all subjects; the normal MCF range for plasma was 14 - 30 mm). The mean change was statistically significant ($p<0.0001$) using a 1-sample t-test for paired observations.

In summary, congenital fibrinogen deficiency is a rare and serious disorder for which the optimal choice among current therapies is not available in the United States. HFC offers distinct advantages over current treatments that are available in the United States with respect to precision of therapeutic effect—infusing only fibrinogen to correct fibrinogen deficiency—and avoidance of potential safety risks associated with cryoprecipitate or plasma therapy.

Moreover, HFC is an answer to the call put forward by both the FDA and the NHF, the leading patient organization for people with bleeding disorders, and its medical committee to address a significant unmet medical need. The clinical efficacy and long safety record indicate that HFC would offer a valuable addition to current treatment options available in the United States for congenital fibrinogen deficiency.

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1.0 INTRODUCTION

1.1 Fibrinogen and fibrinogen deficiencies

Fibrinogen is a plasma glycoprotein and the precursor of fibrin, which is essential for the formation of a blood clot. Fibrinogen is synthesized in hepatocytes as a dimer with 3 pairs of polypeptide chains (designated as Aα, Bβ, and γ), which are encoded as separate genes on chromosome 4; carbohydrate side chains are added before secretion into the plasma [Crabtree 1983, Spraggon 1997]. Transcription leading to the synthesis of these polypeptides is responsive to such conditions as acute phase reactions, pregnancy, injury, or chronic inflammation [Crabtree 1983, Fuller 2001, Liu 1995].

In blood coagulation, the last step in the enzymatic activation cascade, initiated by damage to a blood vessel wall, is the formation of cross-linked fibrin. In this step, thrombin binds to fibrinogen and cleaves the polypeptides to form fibrin monomers. Subsequently, spontaneous fibrin polymerization occurs, as factor XIIIa facilitates cross-linking to form a fibrin clot [Chernysh 2008]. Various genetic mutations affect formation of the polypeptide chains, the rate of synthesis, the ability to bind thrombin, the ability of fibrin to polymerize, and cross-linking. Fibrinogen deficiencies may result in uncontrolled bleeding after trauma or in spontaneous bleeding; they may also be indicated by absent or delayed clot formation in the clotting tests prothrombin time (PT), partial thromboplastin time (PTT), and thrombin time (TT). The lack of fibrinogen also causes impaired aggregation of platelets at the site of injury that makes bleeding worse. Similarly, abnormal and dysfunctional fibrinogen may result in the formation of a poor or unstable clot, leading to a bleeding tendency and abnormal specific coagulation laboratory test results. In addition, some fibrinogen defects or deficiency can lead, paradoxically, to increased thrombus formation and thromboembolism.

Congenital fibrinogen deficiencies are rare hereditary disorders that include the absence of detectable levels of plasma fibrinogen (afibrinogenemia); reduced amounts of plasma fibrinogen (hypofibrinogenemia); and normal amounts of plasma fibrinogen but the fibrinogen itself is

dysfunctional (dysfibrinogenemia). Occasionally, the combination of both reduced amounts and dysfunctional fibrinogen (hypodysfibrinogenemia) is observed. The prevalence of congenital fibrinogen deficiency in the general population is estimated to be approximately 1 per million [de Moerloose 2008, Mannucci 2004]; therefore, the estimated prevalence in the United States is approximately 300 patients. Congenital fibrinogen deficiencies may be evident at an early age and may result in variable clinical manifestations. Some are asymptomatic, whereas others produce severe or fatal bleeding events.

Bleeding due to afibrinogenemia usually manifests in the neonatal period, with 85% of cases presenting with umbilical cord bleeding. However, a later age of onset is not unusual [Lak 1999]. The most common cause of death in afibrinogenemic patients is intracranial bleeding [Martinez 1997]. In one review, one third of the deaths in these patients were due to intracranial bleeding [Henselmans 1999]. Bleeding events may also affect the skin, mucosa, muscles, joints, and gastrointestinal (GI) tract [Acharya 2004]. Joint hemorrhage affects about 54% of afibrinogenemic patients [Lak 1999]. Moderate to severe bleeding may occur after mild trauma or minor surgery. In affected women, menorrhagia is common, and abruptio placenta and spontaneous abortions are seen during pregnancy [Lak 1999, Martinez 1997]. The latter effects may reflect poor implantation, as is observed in fibrinogen-knockout mice, where gestation cannot be maintained to term [Iwaki 2002]. Postpartum hemorrhage has also been observed in afibrinogenemic women [Kobayashi 1996].

Some patients with hypofibrinogenemia often do not experience symptoms. However, they may bleed profusely when hemostatically challenged (eg, with surgery or trauma) or if they have another hemostatic abnormality, and loss of pregnancy can occur.

Dysfibrinogenemia is characterized by approximately 300 different genetic variants, about half of which are clinically silent [Martinez 1997]. A registry study conducted by the Fibrinogen Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis identified approximately 250 reported cases of dysfibrinogenemia, of which 55% were asymptomatic, 25% had bleeding events, and 20% had evidence of

thrombosis [Haverkate 1995]. A subgroup of dysfibrinogenemic patients have both bleeding and thromboembolic complications [Martinez 1997, Roberts 2001].

1.1.1 Paradoxical thrombosis in fibrinogen deficiencies

A growing body of evidence indicates that, despite the absence of fibrinogen, patients with fibrinogen deficiency may develop thromboembolic complications, with or without fibrinogen replacement therapy. These complications may develop in the presence of thrombophilic risk factors, such as protein C deficiency [De Mattia 1993, Hanano 1992], but most patients have no identifiable risk factors.

Korte and Feldges [1994] reported on a patient with congenital afibrinogenemia who showed increased prothombin activation, indicative of increased thrombin formation and a possible prothrombotic state. This abnormality was reversed with fibrinogen substitution. Chafa et al [1995] found ischemic necrosis in the toes and fingers of a woman with congenital severe hypofibrinogenemia and no concomitant thrombotic risk factors. In the registry study of 250 patients with dysfibrinogenemia, Haverkate and Samama [1995] reported that 20% of patients had evidence of thrombosis. Lak et al [1999] reported on a large series of 55 Iranian patients with congenital afibrinogenemia, 2 of whom (a 5-year-old boy and a 14-year-old girl) suffered spontaneous thrombotic events. Dupuy et al [2001] found afibrinogenemia to be "a vascular risk factor" predisposing a 30-year-old man to embolized clots causing ischemic lesions of the toes; at the time of his presentation, he had not received fibrinogen replacement therapy for several years. Roqué et al [2004] observed signs of a "paradoxical prothrombotic state," including placental infarction, in 2 pregnancies in a woman with congenital afibrinogenemia, despite prophylactic treatment with cryoprecipitate.

Recently, Simsek et al [2008] performed a genetic analysis on a congenitally afibrinogenemic man from Turkey who had suffered multiple thromboembolic events. The investigators found a rare homozygous mutation in the Aα chain gene, which normally codes for one of the three fibrinogen chains. Because the patient had no other known thrombogenic risk factors, the

investigators concluded that the genetic defect responsible for afibrinogenemia was also probably associated with thrombosis.

Several hypotheses have been proposed to explain the thromboembolic risk associated with congenital fibrinogen deficiency. In the absence of fibrinogen, platelet aggregation is still possible due to the action of von Willebrand factor (vWF) [De Marco 1986]. Some evidence further suggests that afibrinogenemia itself produces a hypercoagulable state by increasing the amount or activity of circulating thrombin [de Bosch 2002, Dupuy 2001, Korte 1994, Mosesson 2003]. Experimental support for this hypothesis was demonstrated in afibrinogenemic mice [Ni 2000], in which intravascular thrombin formed at the site of induced injury and then embolized downstream. Two mechanisms may explain most of the cases of thrombosis associated with dysfibrinogenemia: 1) abnormal fibrinogen is defective in binding thrombin, which results in elevated thrombin levels; 2) abnormal fibrinogen forms a fibrin clot that is resistant to fibrinolytic degradation [de Moerloose 2008].

There is also evidence indicating that fibrinogen in concentrates used for replacement therapy may reduce circulating thrombin and thrombosis [Dupuy 2001, Korte 1994]. On the other hand, cryoprecipitate, which contains vWF, may actually be more conducive to thromboembolic events by increasing platelet aggregation [Roqué 2004].

1.2 Current treatment of congenital fibrinogen deficiencies

Fibrinogen replacement therapy is effective in the treatment and prevention of bleeding episodes in congenital fibrinogen deficiencies. Fibrinogen preparations are vital for patients with fibrinogen deficiencies, particularly for patients with severe deficiencies. In the United States, cryoprecipitate and plasma are the only available treatment options for congenital fibrinogen deficiencies. However, there are no prospective clinical studies to support the efficacy and/or safety of cryoprecipitate in the treatment of fibrinogen deficiencies.

Cryoprecipitate, currently the preferred treatment in the United States [Acharya 2004], is prepared from plasma that is thawed under controlled conditions at 4°C, the temperature at which certain plasma proteins precipitate—hence the name cryoprecipitate. Each unit of cryoprecipitate contains higher molecular-weight proteins, mainly fibrinogen (150–250 mg, 200 mg on average) and vWF with its associated factor VIII (~80 units), as well as factor XIII and fibronectin. One unit of cryoprecipitate (10–20 mL, 15 mL on average) can be expected to raise plasma fibrinogen by 5 to10 mg/dL [Lopez-Plaza 2008]. Each unit of plasma contains at least 250 mg of fibrinogen, and 1 unit (200–300 mL, 250 mL on average) is reported to raise plasma fibrinogen by 7 to 10 mg/dL in a 70-kg recipient [Silvergleid 2008].

Doses and duration of fibrinogen replacement therapy are dependent on the purpose of replacement therapy, the patient's bleeding history or type of bleeding, or operative procedure. The UK guidelines on therapeutic products for coagulation disorders provide treatment recommendations [Bolton-Maggs 2004]. According to these guidelines, fibrinogen levels should be increased to 100 mg/dL to treat a bleeding episode (and maintained above this threshold until hemostasis is secure) and above 50 mg/dL until wound healing is complete (7–10 days).

Large volumes and multiple units of cryoprecipitate or plasma must be used to maintain these target fibrinogen levels. To increase the fibrinogen level to 100 mg/dL in an afibrinogenemic patient, a fibrinogen dose of 50–70 mg/kg body weight is indicated. Therefore, for an adult weighing 70 kg (3500 mg dose), approximately 17 units of cryoprecipitate (255 mL) need to be pooled and infused within 4 hours; for a neonate weighing 5 kg, 2 units of cryoprecipitate (30 mL) need to be infused. The amount of plasma required in an adult would be 14 units on average (approximately 3000 mL).

Prophylactic therapy may be required for successful completion of pregnancy in women with afibrinogenemia; fibrinogen replacement must be initiated before 5 weeks' gestation and maintained at >100 mg/dL throughout the pregnancy to prevent spontaneous abortion. Fibrinogen consumption increases markedly as gestation progresses, and the amount and

frequency of fibrinogen infusion must be increased accordingly. A plasma level >150 mg/dL is recommended for delivery [Kobayashi 2000].

Patients with hypofibrinogenemia typically have levels of fibrinogen around 100 mg/dL, which theoretically is high enough to protect them against spontaneous bleeding and to enable uneventful pregnancies. Severe hypofibrinogenemia is defined as plasma levels <50 mg/dL but >10 mg/dL; for these patients, fibrinogen replacement therapy may be needed to treat trauma-induced bleeding, a hemostatic challenge (eg, surgery), or an associated hemostatic abnormality [de Moerloose 2008].

Some dysfibrinogenemia patients, particularly those with fibrinogen levels <100 mg/dL (hypodysfibrinogenemia), have an increased frequency of bleeding. These patients may need replacement therapy similar to that required for the treatment of afibrinogenemia.

In many developed countries with market approval of fibrinogen concentrates[1], cryoprecipitate or plasma use is steadily declining. In Europe, cryoprecipitate usage for fibrinogen deficiency occurs only in the United Kingdom, Ireland, and Scandinavian countries; Ireland may soon limit its use. Currently, 4 fibrinogen concentrates are commercially available, namely Clottagen® from LFB (France); Fibrinogen HT® from Benesis (Japan); FibroRAAS® from Shanghai (China); and Haemocomplettan® P from CSL Behring (Germany). Fibrinogen concentrate, where available, is the treatment of choice outside the United States [Santagostino 2000].

CSL Behring's fibrinogen concentrate was developed by Behringwerke (a predecessor to CSL Behring) and has been approved and used under the trade name of Haemocomplettan® P in Germany and Austria since 1986 for both congenital and acquired hypofibrinogenemia. This fibrinogen concentrate has also been licensed in 10 other countries as Haemocomplettan and is available in Canada under the Special Access Program.

[1] In this document, "HFC" is used for the CSL Behring product, human fibrinogen concentrate, whereas references to "fibrinogen concentrates" are generic, and the concentrates may include other products as well as HFC.

2.0 UNMET MEDICAL NEED

Fibrinogen concentrates are the preferred treatment in many countries outside the United States because of demonstrated and potential advantages when compared with cryoprecipitate and plasma in terms of safety, efficacy, access to timely intervention, and precise dosing. The disadvantages of using cryoprecipitate and plasma are detailed below.

Immune reactions

Immune reactions are caused by the interaction of antibodies and the corresponding antigen. These can occur by different mechanisms, including pre-existing IgE or IgG antibody in the patient that reacts with allergens or proteins (including IgA and other normal plasma constituents) in the transfused plasma or cryoprecipitate. The clinical presentations can be subdivided into severe allergic (anaphylactic/anaphylactoid), allergic, hemolytic, and transfusion-related acute lung injury (TRALI).

- *Anaphylactic/anaphylactoid reactions.* Although severe and potentially life threatening, these reactions are uncommon, with an occurrence rate of 1 in approximately 30,000 transfusions, 66% of which followed plasma or platelet transfusion [Domen 2003]. The interventions required for the treatment of allergic reactions not only interrupt the needed fibrinogen replacement therapy, but also may increase the length of hospital stay and the likelihood of additional side effects.
- *Other allergic reactions.* The presence of large amounts of unwanted and unnecessary proteins in plasma and cryoprecipitate cause allergic reactions (such as itching, hives, rash, etc) in 20% to 30% of patients [Acharya 2004, Consensus Conference 1985, McVerry 1979, Silberstein 1989, Sonntag 1997, Wolff 1980]. These allergic reactions are less severe and can be treated with antihistamines. Often, transfusions are discontinued until the patient's symptoms are controlled with antihistamine treatment.
- *Hemolysis.* Both plasma and cryoprecipitate contain anti-A and anti-B antibodies; therefore, the use of ABO-compatible units is preferable, especially in small children or when the infused volume is large relative to the recipient's red cell mass. If large volumes of ABO-incompatible plasma or cryoprecipitate are administered, intravascular hemolysis can occur

[Lopez-Plaza 1995]. A purified product has negligible amounts of anti-A or anti-B antibodies.

- *TRALI.* This is a life-threatening complication of hemotherapy, defined as an acute respiratory reaction occurring in association with transfusion of blood components. Though the reported incidence varies from 1 in 1120 [Silliman 2003] to 1 in 74,000 plasma unit transfusions [Chapman 2008], TRALI is the leading cause of death associated with transfusion of blood components in the United States. Management of TRALI is supportive, with oxygen and cardiovascular support being the mainstay of therapy. Patients who survive the acute event are likely to make a full recovery over a period of days.

Fluid overload

Compared with HFC, larger volumes of plasma are required to achieve the plasma fibrinogen level of 100 mg/dL with a dose of 50 mg/kg body weight. For an average 70-kg adult, the required volume to achieve the recommended plasma fibrinogen level is approximately 3500 mL (~250 mg/250 mL) of plasma. Clinical studies have indicated that large plasma infusion volumes can increase the risk of transfusion-associated circulatory overload (TACO) [Popovsky 2001]. It has been estimated that TACO occurs in approximately 1 in 100 to 1 in 10,000 transfusions [Fiebig 1999]. Fibrinogen deficient children are among the patient groups shown to be at increased risk for TACO [Popovsky 2001].

Viral infection risks

Many well-recognized viruses, including hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), human immunodeficiency viruses-1/2 (HIV-1/2), human parvovirus B19 (B19V), and other blood-borne viruses, have been shown to be transmissible by transfusion of blood components. The combination of strict donor selection and the use of sensitive testing of each donation to detect evidence of viral infections have reduced the risk of infection in recent years. Nevertheless, there is still a potential risk of virus transmission associated with transfusion of either plasma or cryoprecipitate due to the lack of virus inactivation/elimination steps. The current risk of HIV and HCV transmission by transfusion is reported to be approximately 1 in 2 million, and the risk for HBV transmission is approximately 1 in 58,000 to 1 in 269,000 in the

United States [Silvergleid 2008]. Although viral transmission through blood products has become rare, the high lifetime exposure to blood products in a patient with congenital fibrinogen deficiency increases the overall virus transmission risk. Among 294 patients included in a North American registry for rare bleeding disorders, transfusion-associated seropositivity was reported for HBV (15.6%); HCV (25%); and HIV (1%) [Acharya 2004].

Thromboembolic complications

Repeated infusion of large amounts of cryoprecipitate to maintain a fibrinogen level >100 mg/dL for 5–7 days (eg, following a surgical procedure or intracranial hemorrhage) or longer periods (eg, high-level dosing during pregnancy in fibrinogen deficiency patients) also results in a cumulative increase in factor VIII and vWF. Such cryoprecipitate regimens have been observed to be associated with increased risk of thromboembolic complications [Roqué 2004].

Precise dosing

Precise dosing is an important factor in the safety and efficacy of fibrinogen replacement therapy, especially when treating fibrinogen deficiencies in children. Exact fibrinogen replacement dosing cannot be determined when either plasma or cryoprecipitate is used. According to the Circular of Information for the Use of Human Blood and Blood Components, each unit of cryoprecipitate should contain ≥150 mg fibrinogen per unit (approximately 15 mL) [American Association of Blood Banks 2002]. However, neither the fibrinogen content nor the volume is actually measured during the manufacturing process.

Product preparation time

Cryoprecipitate and plasma are stored frozen at −18°C. Thus, thawing and then pooling, in addition to ABO blood type matching, are required prior to plasma infusion. Hospital records have indicated that these activities require more than 1–2 hours and significantly delay replacement therapy. For patients with intracranial hemorrhage, any delay in replacement therapy can lead to more structural brain damage with poor clinical outcome.

Other considerations

Additional practical concerns regarding the use of plasma and cryoprecipitate for the treatment of fibrinogen deficiencies include increased costs to the health care system from blood typing and increased administration and monitoring time compared with the concentrated and purified factor products.

3.0 PRODUCT DESCRIPTION AND CHARACTERIZATION

3.1 Product composition

Fibrinogen, or blood coagulation factor I, is a soluble glycoprotein circulating in plasma as the precursor of fibrin. The active ingredient in HFC is fibrinogen, obtained from human plasma. This fibrinogen is isolated and purified from cryoprecipitate, and is then rapidly processed to the final bulk solution, to which stabilizers are added. This bulk solution is then lyophilized to the final sterile product.

HFC is supplied in a single-use vial containing approximately 1 g of fibrinogen. All of the excipients are well-known physiologic compounds that are used in manufacturing processes of CSL Behring's human plasma products. The composition of the vial's contents is summarized in **Table 1**.

Table 1. Composition of HFC

Components	Function	Content
Human fibrinogen	Active ingredient	900 to 1300 mg*
Human albumin	Stabilizer (protein)	400–700 mg
L-Arginine hydrochloride	Stabilizer (amino acid)	375–660 mg
Sodium chloride	Electrolyte	200–350 mg
Sodium citrate	Electrolyte	50–100 mg

*Actual amount is listed on the vial.

3.2 Proposed indication and proposed US trade name

The proposed indication is for the "treatment of congenital fibrinogen deficiency." The proposed trade name in the United States is Riastap™.

3.3 Dosing

Median recovery results of the pivotal study 2001 predicted that a dose of 70 mg/kg body weight would increase the concentration of fibrinogen by 120 mg/dL, which exceeds the minimal hemostatic level of 100 mg/dL (normal range 200–450 mg/dL [Kreuz 2005]). (In this study, mean baseline fibrinogen level was <20 mg/dL and mean maximum concentration was 130 mg/dL.)

Determination of the patient's fibrinogen level is recommended before and during treatment with HFC.

Initial Dose: If the patient's fibrinogen level is not known, the recommended dose is 70 mg/kg body weight to be administered intravenously.

Subsequent Dose: A target level of 100 mg/dL for minor bleeding events (eg, epistaxis, intramuscular bleeding, or menorrhagia) should be maintained for ≥3 days. A target level of 150 mg/dL for major bleeding events (eg, head trauma or intracranial hemorrhage) should be maintained for 7 days.

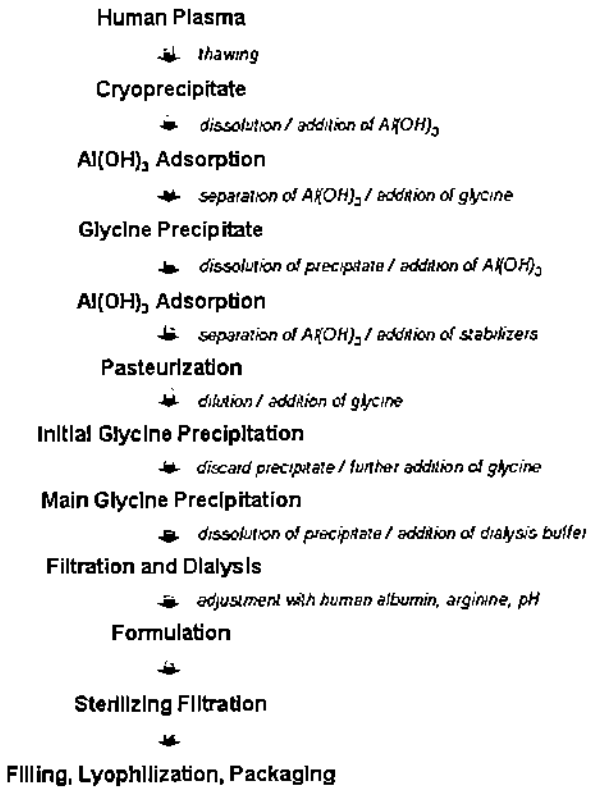
$$\text{dose of fibrinogen (mg/kg body weight)} = \frac{\text{target level (mg/dL)} - \text{measured level (mg/dL)}}{\text{1.7 mg/dL per mg/kg}}$$

3.4 Manufacturing and virus safety

Human plasma, the starting material of HFC, is collected from healthy US donors who meet the Food and Drug (FDA) Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents (21 CFR Parts 606, 607, 610, 640, 660, and 809). All plasma used in the manufacture of HFC is tested using serological assays for hepatitis B virus surface antigen (HBsAg) and antibodies to HIV-1/2 and HCV. The plasma is also tested with nucleic acid testing (NAT) for HCV and HIV-1 and found to be non-reactive (negative). In addition, the plasma is tested by NAT for HAV and B19V. Only plasma that passes virus screening is used for production, and the limit for B19V in the fractionation pool is set not to exceed 10^4 IU of B19V DNA per milliliter.

HFC is manufactured from cryoprecipitate into a glycine precipitate, which is further purified by multiple precipitation/adsorption steps. Pasteurization (heat treatment in aqueous, stabilized solution at 60°C for 20 hours) is integrated into the manufacturing process for virus inactivation, and is followed by 2 glycine precipitation steps (initial and main glycine precipitation). **Figure 1** shows the manufacturing process of HFC.

Figure 1. Manufacturing process of HFC



The virus reduction capacity of the manufacturing process was investigated via virus spike experiments using a scaled-down version of the manufacturing process that replicated the large-scale purification process as closely as possible. Using the reduction factors for each of the manufacturing steps, mean overall reduction factors were calculated for the viruses studied **(Table 2)**.

Table 2. Cumulative (log_{10}) virus inactivation/reduction in HFC

Manufacturing Step	Virus Reduction Factor (log_{10})							
	Enveloped Viruses					Non-enveloped Viruses		
	HIV	BVDV	WNV	HSV-1	PRV	HAV	CPV	B19V
Cryoprecipitation	n.d.	n.d.	n.d.		1.6[a]	2.4	2.8	n.d.
$Al(OH)_3$ adsorption/ glycine precipitation/ $Al(OH)_3$ adsorption	(2.8)[b]	(1.5)[b]	n.d.	(0.9)[b]				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)[b]	(1.6)[b]	n.d.
Cumulative virus reduction (log_{10})	**≥ 9.6**	**≥ 11.2**	**≥ 8.3**	**≥ 9.1**	**1.6**	**≥ 6.7**	**4.4**	**≥ 4.5**

B19V = human parvovirus B19; BVDV = bovine viral diarrhea virus (model for HCV); CPV = canine parvovirus (model for B19V); HAV = hepatitis A virus; HCV = hepatitis C virus; HFC = human fibrinogen concentrate; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; NA = not available; n.d. = not done; PRV = pseudorabies virus; WNV = West Nile virus.
[a] PRV—similar to HSV-1, a herpes virus—is reduced by cryoprecipitation by 1.6 log_{10}.
[b] Not included in the calculation of the cumulative virus reduction factor.

The results of the virus validation studies demonstrate the very efficient and robust reduction of a wide range of enveloped and non-enveloped viruses by pasteurization, as well as the reliable contribution to overall virus reduction by the other steps investigated. In additional studies, the effective inactivation by pasteurization was also demonstrated for West Nile virus (WNV), with a reduction factor of ≥8.3 log_{10}, and for B19V, with a reduction factor of ≥4.5 log_{10}.

4.0 HFC DEVELOPMENT OVERVIEW

4.1 CSL Behring background

The sponsor, CSL Behring, is a leading producer of plasma protein biotherapies and produces and markets 10 coagulation factor products worldwide, including HFC. These products are derived from plasma or produced via recombinant protein production technology.

4.2 Regulatory history

Because of the rarity of congenital fibrinogen deficiency, a clinical development program with comparator- or placebo-controlled prospective clinical trials to prove efficacy and safety of HFC for this indication is not feasible. HFC has been available outside of the United States for more than 20 years. At the time of original market application approval in Europe, controlled prospective clinical trials were not required for all indications. Until fairly recently, a stricter regulatory environment in the United States has precluded submission of a market application for HFC. For this reason, HFC was available for more than 15 years in Europe before discussion began regarding development for the US market.

In an initial pre–investigational new drug (IND) meeting in 2002, CSL Behring (known at the time as Aventis Behring) met with Center for Biologics Evaluation and Research (CBER), Office of Blood Research and Review (OBRR) representatives to discuss appropriate clinical studies for FDA approval of HFC for the treatment of congenital fibrinogen deficiency. During that meeting, OBRR representatives suggested that a retrospective survey of physicians be conducted to gather information concerning current treatments for fibrinogen deficiency, target fibrinogen levels, and bleeding events. The physician survey could be used as a historical control for an efficacy study. CSL Behring conducted this survey (Study 1221) between October 2002 and March 2003.

In June 2005, participants at the FDA's Biological Therapeutics for Rare Plasma Protein Disorders Public Workshop acknowledged the need for more flexible standards of clinical trial design to encourage the development of therapies for rare plasma protein disorders. During this workshop and in subsequent meetings with OBRR representatives, the clinical development of HFC was further discussed. OBRR representatives told CSL Behring to facilitate approval the company should conduct a clinical development program that included a clinical study with a surrogate efficacy end point to support product approval for the treatment of congenital fibrinogen deficiency. With the accelerated approval program, a post-approval efficacy study to verify the surrogate end point would be required (Subpart E, 21 CFR 601.41).

Therefore, to be considered for an accelerated approval, CSL Behring developed a clinical program for HFC that included 3 studies:

- The retrospective survey of physicians (Study 1221)
- A pivotal pharmacokinetic (PK) efficacy and safety study that used maximum clot firmness (MCF) as a surrogate end point for hemostatic efficacy (Study 2001)
- A post-marketing safety and efficacy commitment study (Study 3001) to demonstrate the hemostatic efficacy of HFC administration and verify a plausible relationship between MCF and hemostatic efficacy

In 2006, OBRR representatives agreed to the proposed clinical program and notified CSL Behring in early 2007 that the pivotal study could begin. In March 2008, orphan drug designation was approved for the indication of treatment of fibrinogen-deficient patients, and a Biologics License Application (BLA) for HFC, with the proposed trade name Riastap™, was submitted in July 2008, shortly after completion of the pivotal study 2001. This application was accepted for filing and granted priority review in August 2008, with a BLA action due date of January 16, 2009. The contingent approval of the BLA would be based on the results of Study 2001 and successful completion of Study 3001.

4.3 Overview of preclinical studies

The efficacy and safety of HFC have been demonstrated in several appropriate animal models (see **Table 3**).

Fibrinogen, the active component in HFC, is a physiologic constituent of human plasma. The pharmacological effect of fibrinogen is well characterized, and fibrinogen has been in clinical use for decades in Europe. Nevertheless, *in vivo* pharmacodynamic, safety pharmacology, and toxicity studies were conducted with HFC. In addition, 2 separate tests for possible neoantigenicity caused by the pasteurization process were conducted. Because there is no reason to suspect mutagenic, teratogenic, or carcinogenic effects of human fibrinogen, such studies were not deemed necessary.

- *Pharmacodynamics*: HFC effectively replaced fibrinogen in a hypofibrinogenemic rat model that mimicked sepsis-induced disseminated intravascular coagulation (DIC). Impaired coagulation and thromboelastography values were reversed by HFC. There were no cases of abnormal thromboelastography values, a measure that might be indicative of thromboembolic risk.
- *Safety pharmacology*: No impairment of major organ systems was demonstrated in anesthetized beagles exposed to supratherapeutic doses of HFC totaling 320 mg/kg body weight. After multiple doses, modest changes in coagulation parameters were observed, in keeping with high plasma fibrinogen levels.
- *Toxicity*: No acute toxic effects were observed following a single, intravenous (i.v.) injection of HFC in rats and mice. Local tolerance of HFC was evaluated after intended i.v. and unintended intra-arterial and paravenous (i.a. and p.v.) administration in rabbits; no findings indicative of toxicity were seen in the *in vivo* study or at necropsy.
- *Neoantigenicity*: Separate studies in rabbits and guinea pigs found no evidence of potential neoantigenicity related to the pasteurization process of HFC.

In summary, these preclinical results demonstrate the efficacy and safety of HFC. Importantly, they show good local tolerability, no neoantigenicity, and no evidence of increased risk for thromboembolic events.

Table 3. Preclinical studies with HFC

Study Type	Route of Administration	Species
Pharmacodynamics	i.v.	Rat
Safety pharmacology	i.v.	Dog (beagle)
Single-dose toxicity	i.v.	Mouse, rat
Local tolerance	i.v., i.a., p.v.	Rabbit
	s.c.	Rabbit
Neoantigenicity	i.c., i.v.	Guinea pig
	i.v.	Rabbit

HFC = human fibrinogen concentrate; i.a. = intra-arterial; i.c. = intracutaneous; i.v. = intravenous; p.v. = paravenous; s.c. = subcutaneous.

4.4 Overview of clinical studies

The HFC clinical program includes 5 completed studies (4 studies in congenital fibrinogen deficiency and 1 in acquired fibrinogen deficiency) in which HFC was administered to a total of 131 subjects **(Table 4)**:

- Study 101: Phase I PK study
- Study 2001: Pivotal phase II study
- Study 501: Phase IV study
- Study 7D-501: Clinical Observational Monitoring Project (COMP)
- Study 402: Virus safety study

In addition, a retrospective survey of physicians (Study 1221) was conducted that included 100 patients receiving treatment for congenital fibrinogen deficiency. The main treatments reported in the clinical survey were HFC, cryoprecipitate, and plasma. A post-marketing commitment study (Study 3001) is ongoing.

The pivotal PK, efficacy and safety study (Study 2001) was conducted according to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) recommendations. The other referenced supportive studies were performed prior to these guidelines but were compliant with the Declaration of Helsinki.

Table 4. Overview of completed clinical studies

Type of Study	Study Identifier	Dates of Study Conduct	Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Total Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Studies in the Indication of Congenital Fibrinogen Deficiency								
PK (Phase I)	101	04/93–11/93	PK of HFC	Multicenter, prospective, open-label, uncontrolled	Single dose of approximately 70 mg/kg b.w. of HFC	6	Patients with congenital fibrinogen deficiency (afib or hypofib)	Single dose
Efficacy and PK (Phase II)	2001	07/07–05/08	Efficacy (using surrogate end point MCF), PK and safety	Multicenter, prospective, open-label, uncontrolled	Single i.v. dose of 70 mg/kg b.w. of HFC	15	Patients with congenital fibrinogen deficiency	Single dose
Efficacy (Phase IV)	501	05/85–02/92	Efficacy and tolerance	Retrospective, multicenter	Single i.v. dose of 63.5 mg/kg b.w., or 2.0 g/patient (therapeutic), or 76.9 mg/kg b.w., or 2.0 g/patient (prophylactic) of HFC	12	Patients with congenital fibrinogen deficiency (afib, hypofib, dysfib)	1 day to 77 months (substitution in an individual bleeding episode or surgical intervention lasted 1 to 12 days)
Clinical survey	1221	10/02–03/03	How often do they bleed? How are they treated for different bleeding events?	Retrospective, multicenter	Fibrinogen concentrate, cryoprecipitate, plasma, recombinant activated factor VII, Humate-P®	100	Patients with congenital fibrinogen deficiency	Major events: 4 to 14 days; Minor events: 1 to 7 days
Virus safety	402	06/85–06/87	Hepatitis virus and HIV safety	Prospective, open-label, uncontrolled	Total i.v. dose of 50 mg/kg – 3.3 g/kg b.w. (single dose of 36–67 mg/kg b.w.) of HFC	6[a]	Patients with any congenital or acquired fibrinogen deficiency or dysfunction	Single dose to 57 weeks
Studies in Other Indications: Acquired Fibrinogen Deficiency								
Efficacy	7D-501	04/91–06/94	Efficacy, tolerance, and safety	Prospective, open-label, uncontrolled COMP	Dosage of HFC was guided by physician assessment of individual therapeutic need	92	Patients with acquired hypofib	Single and multiple dose (up to 12 days)

afib = afibrinogenemia; b.w. = body weight; COMP = Clinical Observational Monitoring Project; dysfib = dysfibrinogenemia; HFC = human fibrinogen concentrate; HIV = human immunodeficiency virus; hypofib = hypofibrinogenemia; i.v. = intravenous; MCF = maximum clot firmness; PK = pharmacokinetic.
[a] Four subjects were analyzed in the original study report; 2 subjects were added to the analysis by a report amendment.

5.0 US CLINICAL DEVELOPMENT PROGRAM

The clinical development program to support HFC consideration for approval in the United States consists of 3 studies:

- Pivotal PK efficacy and safety study (Study 2001)
- Retrospective survey of physicians (Study 1221)
- Post-marketing efficacy and safety commitment study (Study 3001)

The pivotal PK clinical study and retrospective survey of physicians have been completed and a summary follows; also summarized is the protocol for the ongoing post-marketing commitment study.

5.1 Pivotal pharmacokinetic, efficacy, and safety study (Study 2001)

5.1.1 Design and objectives

Patients with congenital afibrinogenemia received a single-dose infusion of 70 mg/kg body weight of HFC in this prospective, open-label, uncontrolled, multicenter study. Subjects were followed for a minimum of 45 days to assess safety.

The objectives were to:

- Compare MCF before and 1 hour after HFC administration (primary end point)
- Determine the single-dose PK of HFC
- Assess the safety of HFC

5.1.2 Methods

5.1.2.1 Dosing

The dose was calculated for each subject based on 70 mg/kg body weight HFC was labeled and supplied as 1 g of fibrinogen. However, each product lot manufactured has a specific fibrinogen

concentration that differs slightly, and the lot used in the 2001 PK study had a fibrinogen concentration of 22 mg/mL after reconstitution (instead of 20 mg/mL). Due to the slightly higher fibrinogen concentration of the PK study lot, the actual median dose of HFC administered in this study was 77 mg/kg body weight. The actual fibrinogen dose (22 mg/mL) administered to each subject was used for the PK analysis. Immediately after reconstitution, the infusion was administered slowly, preferably with a perfusor, at a rate not exceeding 5 mL/min (mean infusion rate was 4.33 mL/min; mean duration of infusion was 56.1 minutes in the intent-to-treat (ITT) population and 58.7 minutes in the safety population). If any reaction occurred that was presumed to be related to infusion, the infusion rate was decreased or the infusion was halted, as appropriate to the clinical condition of the subject.

5.1.2.2 Measurements

The change in MCF from before fibrinogen infusion (baseline) to 1 hour after infusion was one primary end point in the 2001 PK study. As a measure of the ability of blood to coagulate, MCF was used as a marker to assess the hemostatic efficacy of fibrinogen replacement therapy in support of the HFC BLA. MCF was determined by rotational thromboelastrometry (ROTEM®) in plasma in the central laboratory at CSL Behring GmbH (Marburg, Germany). MCF depends on the activation of coagulation, plasma fibrinogen concentration, and polymerization and cross-linking of the fibrin matrix and is directly influenced by the fibrinogen concentration of the plasma sample.

ROTEM® is one of several viscoelastic tests of clot formation; others include the thromboelastograph (TEG®) (Haemoscope) and Sonoclot® (Sienco). TEG®, which was first used in the 1940s, is commonly used in the United States. The basic principle of this technology is to measure the motion of a pin suspended in a blood sample in relation to a slowly oscillating cup that contains the blood sample [Artang 2000, Carroll 2008]. As the sample clots, the clot physically links the cup to the pin and, as the clot becomes stronger and more stabilized, the movement of the cup and the pin become more synchronized. The pin movement is converted to a thromboelastogram tracing, which reflects the physical properties of clot formation, including

the time to onset of clotting and the kinetics, strength, and dissolution of the clot. ROTEM® (Pentapharm GmbH) has been used for decades outside of the United States, and Pentapharm is currently seeking FDA approval for this technology in the United States. ROTEM® applies similar principles to TEG®; the main difference is that the pin is suspended in a stationary cuvette. The pin is fixed to an axis that rotates back and forth, and when the clot forms, the rotation of the pin and axis is reduced. (For a more detailed description and the advantages of ROTEM®, see **Appendix I.**)

Rationale for using MCF measured by ROTEM®

Historically, physicians have used plasma fibrinogen levels in the clinical management of patients with fibrinogen deficiency. However, MCF testing with ROTEM® provides a more convenient method to monitor hemostasis. Advantages include rapidity of measurement [Simioni 2008] and accuracy. ROTEM® has been shown to predict clinical coagulopathy [Cammerer 2003, Davis 1995, Kaufmann 1997, Martin 1991, Spiess 1987], and MCF measured by ROTEM® has been shown to be a functional marker for fibrinogen activity and the effects of fibrinogen replacement on clinical efficacy [De Lorenzo 2006, Fenger-Eriksen 2005, Fries 2006, Fries 2005].

Other measurements and assessments

Plasma fibrinogen activity was determined by the Clauss method and antigen method (enzyme-linked immunosorbent assay [ELISA]) in the central laboratory of CSL Behring for the pivotal PK study (Study 2001). The Clauss assay is the conventional method for measuring the functionally active fibrinogen fraction, rather than the total fibrinogen levels. It is a reliable, accurate, and precise method for determining fibrinogen function. ELISA is a fibrinogen-specific assay using paired antibodies for fibrinogen antigen.

Fibrinogen activity levels were determined by the Clauss and ELISA methods at pre-infusion and at 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216, and 312 hours after the end of infusion. PK parameters were calculated for plasma fibrinogen.

Safety was assessed through reports of AEs, hematology and biochemistry, measures of activation of coagulation and viral antibodies, viral serology, polymerase chain reaction (PCR) for viruses, vital signs, and physical examinations.

5.1.3 Major inclusion and exclusion criteria

The major inclusion criteria were congenital afibrinogenemia with plasma fibrinogen activity and antigen undetectable at screening (ie, <20 mg/dL) and age ≥6 years. Major exclusion criteria included other bleeding disorders, administration of fibrinogen concentrate or other fibrinogen-containing blood product within 2 weeks prior to enrollment, acute bleeding, and a history of deep vein thrombosis (DVT), pulmonary embolism, or arterial thrombosis (as per original protocol) within 1 year prior to enrollment (as per substantial amendment No. 1).

5.1.4 Results

5.1.4.1 Demographics and baseline characteristics

A total of 15 subjects (5 females and 10 males) were studied at 5 centers in the United States (7 subjects) and 5 centers in Italy (8 subjects) in 2007 and 2008 **(Table 5)**. Four subjects were <16 years of age and 11 were 16 to 61 years of age (overall mean of 30 years and range of 8 to 61 years). The body mass index (BMI) ranged from 16.6 to 29.2 and weight from 29 to 94 kg. Thirteen were Caucasian, 1 was Asian, and 1 was Native American or an Alaskan native.

Table 5. Study 2001 baseline characteristics

Characteristic	n (%)	Mean ± SD
Gender		
Female	5 (33.3)	
Male	10 (66.7)	
Age (years)		29.5 ± 15.9
Age group (years)		
<16	4 (26.7)	
16 to <65	11 (73.3)	
≥65	0 (0.0)	
Race		
Caucasian	13 (86.7)	
Asian	1 (6.7)	
Native American or Alaska Native	1 (6.7)	
Ethnic group		
Hispanic or Latino	10 (66.7)	
Non–Hispanic or Latino	5 (33.3)	
Weight (kg)		66.6 ± 19.3
BMI (kg/m^2)		23.85 ± 3.81

BMI = body mass index; SD = standard deviation.

5.1.4.2 Primary efficacy end point, MCF

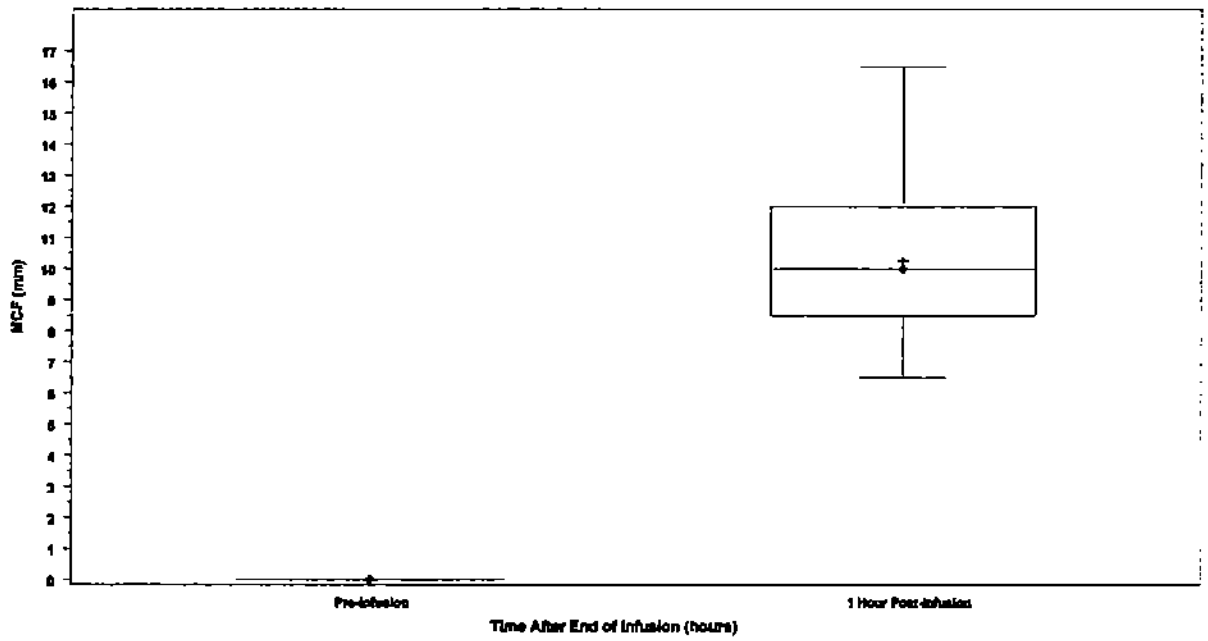
The mean MCF (± SD) at 1 hour post-infusion was 10.3 ± 2.7 mm for the 13 subjects who had complete data; at baseline MCF was 0 for all subjects (**Table 6; Figure 2**) (Note: The normal MCF range for plasma was 14 – 30 mm). The mean change was statistically significant (p<0.0001) using a 1-sample t-test for paired observations. Similar efficacy results were seen across sub-analyses by gender, age, and country.

Table 6. MCF (mm) (ITT population)

Time point	N	Mean ± SD	Median (range)	p value[a]
Pre-infusion	13	0 ± 0	0 (0-0)	--
1 hour post-infusion	13	10.3 ± 2.7	10.0 (6.5-16.5)	--
Mean change (primary analysis)	15	8.9 ± 4.4	9.5 (0-16.5)	<0.0001

ITT = intention to treat; MCF = maximum clot firmness; SD = standard deviation.
[a] 2-sided p value from 1-sample t-test.

Figure 2. Course of MCF[a] (ITT population)



ITT = intention-to-treat; MCF = maximum clot firmness.
[a] Only non-missing data are shown (ie, imputed changes due to missing MCFs are not shown).

5.1.4.3 Pharmacokinetics

PK data are available for 14 of the subjects **(Table 7)**. Plasma fibrinogen activity determined by the Clauss method reached a maximum level within 1 hour post-infusion and decreased below the detection limit (<20 mg/dL) by day 10 **(Figure 3)**. Fibrinogen plasma antigen levels determined by the ELISA method reached a maximum level within 30 minutes post-infusion (mean and median of 130 mg/dL) and decreased to 110 mg/dL by day 14. Fibrinogen mean activity levels (Clauss) and corresponding mean antigen levels (ELISA) for each PK time point are included in **Table 8**. Fibrinogen activity and fibrinogen antigen levels were strongly correlated.

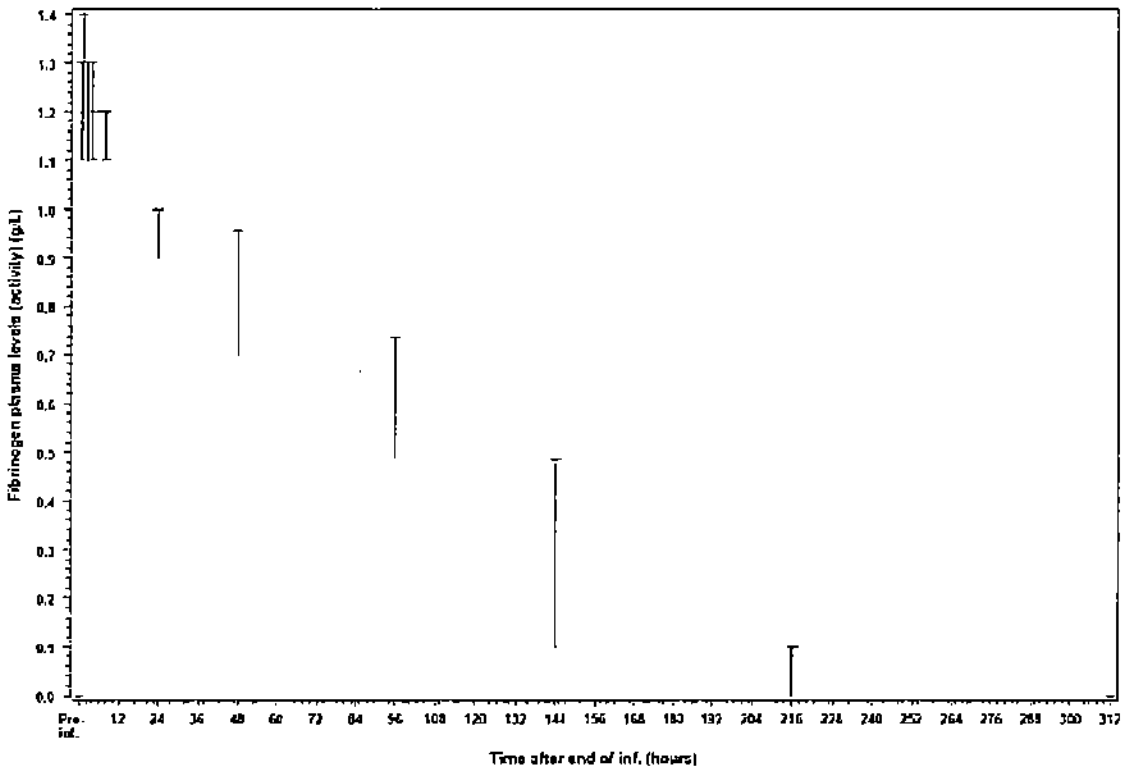
The median fibrinogen activity incremental *in vivo* recovery (IVR) was 1.7 mg/dL (1.30–2.73) with a mean of 1.8 mg/dL (± 0.35 SD) increase per mg/kg body weight. The median fibrinogen antigen incremental IVR was 1.7 mg/dL (1.28–2.45) with a mean of 1.7 mg/dL (± 0.31 SD) increase per mg/kg body weight.

Table 7. PK parameters for fibrinogen activity (PK PP population)

Parameter	Mean ± SD	Median (range)
$t_{1/2}$ (h)	78.7 ± 18.13	77.1 (55.73–117.26)
C_{max} (mg/dL)	140 ± 27	130 (100–210)
AUC for dose of 70 mg/kg b.w. (h*mg/mL)	124.3 ± 24.16	126.8 (81.73–156.40)
Extrapolated part of AUC (%)	8.4 ± 1.72	7.8 (6.13–12.14)
CL (mL/h/kg)	0.59 ± 0.13	0.55 (0.45–0.86)
MRT (h)	92.8 ± 20.11	85.9 (66.14–126.44)
V_{ss} (mL/kg)	52.7 ± 7.48	52.7 (36.22–67.67)

AUC = area under the concentration-time curve; b.w. = body weight; CL = clearance; C_{max} = maximum concentration within 4 hours; h = hours; MRT = mean residence time; PK PP = pharmacokinetic per-protocol; SD = standard deviation; $t_{1/2}$ = terminal elimination half-life; V_{ss} = volume of distribution at steady state.

Figure 3. Median (Q25–Q75) fibrinogen plasma activity levels (ITT population)



inf. = infusion; ITT = intent-to-treat; Q25 = 25% quartile; Q75 = 75% quartile.
Conversion: 1 g/L = 100 mg/dL.

Table 8. Fibrinogen activity, Clauss and Antigen/ELISA assays (ITT population)

Time (hours)	Fibrinogen Activity (mg/dL) Clauss Assay (Mean ± SD)	Fibrinogen (mg/dL) Antigen, ELISA (Mean ± SD)
Pre-infusion	<20 ± 0	3 ± 3
0.5	130 ± 28	130 ± 26
1	130 ± 29	130 ± 25
2	130 ± 25	120 ± 24
4	120 ± 24	110 ± 20
8	120 ± 18	100 ± 22
24	95 ± 14	85 ± 11
48	84 ± 13	70 ± 10
96	62 ± 16	50 ± 15
144	32 ± 18	30 ± 9
216	<20 ± 8	22 ± 7
312	<20 ± 4	11 ± 4

ELISA = enzyme-linked immunosorbent assay; ITT = intent-to-treat; SD = standard deviation.

5.1.4.4 Safety

Safety results are presented in section 8.0.

5.1.5 Conclusions

The mean MCF (± SD) at 1 hour post-infusion was 10.3 ± 2.7 mm for the 13 subjects who had complete data (Note: At baseline MCF was 0 for all subjects; the normal MCF range for plasma was 14 - 30 mm). The mean change was statistically significant ($p<0.0001$) using a 1-sample *t*-test for paired observations. The PK results for fibrinogen activity were consistent with those observed in a previous PK study (Study 101) conducted in 6 subjects with severe congenital fibrinogen deficiency (afibrinogenemia or severe hypofibrinogenemia), 5 of whom were eligible for PK analysis (see Section 6.1).

5.2 Retrospective survey of physicians (Study 1221)

5.2.1 Design and objectives

This survey was designed to obtain information about patients with congenital fibrinogen deficiency. The objectives of the survey were to:

- Find out how often these patients bleed, what treatments they generally receive, how they are treated for different bleeding events, and target fibrinogen levels for treatments
- Summarize current opinions regarding treatment from physicians experienced with the disease.

The content of the survey was reviewed by and agreed upon with CBER.

5.2.2 Methods

The standardized questionnaire consisted of a general and a patient-specific part and was sent to physicians or hemophilia treatment centers known to treat patients with congenital fibrinogen deficiency in the United States and nine other countries. The general part collected data about the 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 prophylaxis and on-demand treatment. In the patient-specific part, physicians recorded specific information about each patient treated, including demographics, the schedule and type of treatments, and details of single events. Results were tabulated for the overall data and separately for the United States and Canada. All statistical analyses were descriptive.

5.2.3 Results

Surveys were collected between October 2002 and March 2003. Data from 34 physicians from 10 countries (United States, 11; Italy, 9; Canada, 3; Austria, 2; Iran, 2; Germany, 2; Spain, 2;

Switzerland, 1; Turkey, 1; and United Kingdom, 1) were included in the database. Data from 3 US physicians who had no experience in the treatment of patients with fibrinogen deficiency were excluded from the analysis. Eight US physicians (13 patients) and 3 Canadian physicians (5 patients) treated a total of 18 patients.

In the survey, the overall number of patients followed by physicians for congenital fibrinogen deficiency was 158. Data from the patient-specific part of the questionnaire were received for 101 patients. Data from 1 patient were excluded because the physician stated that this patient was treated only once, was bleeding frequently, and was usually treated in a different center.

In summary, the survey included 31 physicians in 10 countries with data from 100 patients with congenital fibrinogen deficiency. Patients included 53 males and 47 females ranging in age from 7 days to 75 years, with a median age of 20.5 years.

5.2.3.1 General questions

The majority of patients (81 of 100 patients overall and 11 of 18 in the United States and Canada) received on-demand treatment; 19 patients received routine prophylaxis; and 5 patients had periods of both on-demand and prophylactic treatment.

The median plasma fibrinogen level for the differentiation between severe and moderate/mild hypofibrinogenemia was 50 mg/dL. The median target plasma fibrinogen levels reported were 100 mg/dL for routine prophylaxis and minor bleeding events and 150 mg/dL for major events. Physicians tended to maintain these levels for 1 to 7 days for minor events and minor surgery and 4 to 14 days for major events.

Eighty-one percent (25 of 31) of the physicians included in the analysis reported using the Clauss method to determine plasma fibrinogen levels. The detection limits for the methods of measurement employed ranged widely (5 mg/dL to 69.7 mg/dL). In response to the question, "What type of products do you use?" 68% (21 of 31) of the physicians included in the analysis indicated fibrinogen concentrates, and 26% (8 of 31) indicated cryoprecipitate. Some physicians

reported using only one treatment, either plasma, recombinant activated factor VII, or factor VIII/vWF.

5.2.3.2 Patient-specific data

Data for 100 patients are included in the analysis **(Table 9)**. Nineteen of the patients were on regular prophylactic treatment. The most common reason for initiating prophylaxis was previous cerebral bleeding. Eighty-nine percent (17 of 19) of prophylaxis patients were receiving fibrinogen concentrates in a single dose of 18 to 120 mg/kg body weight, with a median of 53 mg/kg body weight, and were treated once a week or less (59%); the two other prophylaxis patients were treated every 2 weeks or monthly. Of the 81 patients receiving on-demand treatment, 42 (52%) were treated with either fibrinogen concentrate or cryoprecipitate; 24 (30%) were treated with only fibrinogen concentrate; 10 (12%) were treated with only cryoprecipitate; 4 (5%) were treated only with other products; and for 1 subject, no product was specified.

Table 9. Baseline characteristics

Characteristic		N[a]	Median	Range	Male (%)
Age (years)	All patients	96	20.5	0–75	
	Fibrinogen[b]	45	26	0–58	
	Cryoprecipitate[b]	43	19	0–64	
	Routine prophylaxis[c]	17	39	5–47	
	On-demand treatment[c]	74	19.5	0–75	
Gender	All patients	100			53
	Fibrinogen[b]	48			52
	Cryoprecipitate[b]	43			54
	Routine prophylaxis[c]	19			53
	On-demand treatment[c]	76			55
Body weight (kg)	All patients	96	57	3–95	
	Fibrinogen[b]	45	58	4–95	
	Cryoprecipitate[b]	43	56	5–80	
	Routine prophylaxis[c]	18	65	21–95	
	On-demand treatment[c]	73	56.5	4–90	
Baseline fibrinogen levels (mg/dL)	All patients	98	6	0–116	
	Fibrinogen[b]	48	10	0–116	
	Cryoprecipitate[b]	42	5	0–89	
	Routine prophylaxis[c]	19	10	0–50	
	On-demand treatment[c]	74	5	0–116	
Duration of care in Center (years)	All patients	95	9	0–40	
	Fibrinogen[b]	44	7	0–40	

Characteristic		N[a]	Median	Range	Male (%)
	Cryoprecipitate[b]	43	14	0–36	
	Routine prophylaxis[c]	16	10	1–40	
	On-demand treatment[c]	74	10	0–36	

[a] Number of subjects with available data; [b] Actual treatment preference of center; [c] Subject's last documented type of treatment.

A total of 517 bleeding episodes (322 spontaneous, 100 trauma-related, 79 surgery-related, and 16 "other" or unspecified) were reported. The mean and median (range) annual incidences of bleeding episodes were 0.5 and 0 (0–2.6), respectively, for patients receiving prophylactic replacement therapy and 0.7 and 0.2 (0–16.5), respectively, for patients receiving on-demand therapy. Fifteen patients had more frequent bleeding **(Table 10)**.

The treating physicians judged both fibrinogen concentrate and cryoprecipitate to have excellent or good hemostatic efficacy for >90% of all events, both in the overall analysis and when the analysis considered the type of bleeding event. Fibrinogen concentrates were used more often than cryoprecipitate for the following bleeding/surgery events: menorrhagia, 30 vs 15 events; intracranial bleeding, 5 vs 2 events; major surgery, 11 vs 5 events; and minor surgery, 29 vs 17 events. Two patients had a thrombotic episode while on prophylactic treatment (one while on cryoprecipitate).

Table 10. Details of individual patients treated on demand with at least one bleeding episode per year

Patient No.	Plasma Fibrinogen Levels (mg/dL)	Duration of Follow-up (years)	No. of Events[a]	Incidence per Year	Treatment Products
1	<10	8.0	11	1.4	Concentrate[b]
2	<10	0.3	3	9.0	Mixed
3	<10	6.9	15	2.1	Mixed
4	<10	0.8	2	2.6	Mixed
5	<10	5.0	18	3.6	Concentrate[b]
6	<10	23.6	61	2.6	Mixed
7	<10	2.8	46	16.5	Mixed
8	<10	0.1	1	7.6	Mixed
9	<10	1.0	1	1.0	Cryoprecipitate
10	<10	0.5	1	2.1	Mixed
11	32	0.5	1	1.8	Other
12	<10	0.2	1	4.2	Concentrate[b]
13	<10	0.9	1	1.0	Concentrate[b]

Patient No.	Plasma Fibrinogen Levels (mg/dL)	Duration of Follow-up (years)	No. of Events[a]	Incidence per Year	Treatment Products
14	<10	3.4	15	4.4	Concentrate[b]
15	89	0.2	1	4.0	Cryoprecipitate

[a] If the first event occurred on the start date of on-demand treatment, it was not taken into account.
[b] "Concentrate" denotes commercial fibrinogen concentrates.

5.2.4 Conclusions

The reported annual incidence of bleeding was low in this survey. Patients were treated mostly with fibrinogen concentrates or cryoprecipitate, with fibrinogen concentrates reported slightly more often. Fibrinogen concentrates and cryoprecipitate were both judged to be effective for restoration of hemostasis. The median target plasma fibrinogen level reported for routine prophylaxis and minor bleeding events was 100 mg/dL; for major bleeding events, it was 150 mg/dL.

5.3 Post-marketing commitment study (Study 3001)

5.3.1 Design and objectives

This is a multinational, multicenter, prospective, open-label, historically controlled, phase IIIb non-inferiority clinical trial of efficacy and safety of HFC for on-demand treatment of acute bleeding in subjects with congenital fibrinogen deficiency.

The primary objective is to demonstrate hemostatic efficacy in patients treated with HFC compared with a historical control group. The historical control group consists of 39 patients treated with cryoprecipitate for 1 or more acute bleeding episodes in the retrospective survey of physicians (Study 1221). This post-marketing study will also verify that MCF, the surrogate end point of pivotal study 2001, has a plausible relationship to hemostatic efficacy. The study is projected to have a 60-month enrollment period and include 23 evaluable subjects who will receive HFC infusions. For each subject, the study duration will be 45 days. The treatment period

with HFC for any subject will be a maximum of 21 treatment days and will be determined by the investigator based on daily fibrinogen levels and severity of bleeding.

The patient population will include individuals with either afibrinogenemia or severe hypofibrinogenemia, defined as plasma fibrinogen levels <50 mg/dL, who present with at least 1 episode of acute bleeding, either spontaneous or after trauma. The primary end point will be an overall clinical assessment of hemostatic efficacy, based on laboratory parameters and the investigators' clinical assessment.

Secondary objectives are to:

- Correlate overall hemostatic efficacy of HFC with MCF
- Demonstrate the ability of HFC to raise plasma fibrinogen levels to a target of 100 mg/dL (minimum 80 mg/dL) for minor bleeding events and 150 mg/dL (minimum 130 mg/dL) for major bleeding events
- Document safety of HFC, including viral safety

5.3.2 Methods

5.3.2.1 Dosing

Each subject will receive at least one infusion for treatment of acute bleeding beginning on Day 1. The appropriate dose (mg/dL) of HFC is to be calculated individually as follows:

$$\text{dose of fibrinogen (mg/kg body weight)} = \frac{\text{target level (mg/dL)} - \text{measured level (mg/dL)}}{\text{1.7 mg/dL per mg/kg}}$$

The target level of 100 mg/dL with an acceptable lower limit of 80 mg/dL for minor events should be reached on at least 3 subsequent days. The target level of 150 mg/dL with an acceptable lower limit of 130 mg/dL for major events should be reached on at least 7 subsequent

days. Subsequent dosing (amount and frequency) will be determined by fibrinogen levels and the investigator's assessment of the subject's clinical requirements.

5.3.2.2 Measurements

Efficacy variables

- Investigator's overall clinical assessment of hemostatic efficacy (based on an established scale used for hemophilia patients **[Table 11]**) 24 hours after the last HFC infusion, in comparison with the hemostatic efficacy of cryoprecipitate (historical data from Study 1221) without knowledge of any MCF results
- MCF assessment at pre-infusion and 1 hour after the end of infusion
- Response and IVR of fibrinogen (fibrinogen plasma levels at pre-infusion, 1, 3, 6, and 12 hours after the end of the first infusion; at pre-infusion and 1 hour after the end of each subsequent infusion; and at the time of the overall clinical assessment of hemostatic efficacy)

Table 11. Rating of hemostatic efficacy

Category	Definition[a]
Excellent	Immediate and complete restoration of hemostasis in the absence of other hemostatic intervention* as clinically assessed by the treating physician; and /or < 10% drop in hemoglobin compared with baseline.
Good	Eventual complete restoration of hemostasis in the absence of other hemostatic intervention* as clinically assessed by the treating physician; and/or < 20% drop in hemoglobin compared with baseline.
Poor	Incomplete restoration of hemostasis and additional hemostatic intervention* required, as clinically assessed by the treating physician; and/or between 20% and 25% drop in hemoglobin compared with baseline.
None	No restoration of hemostasis and alternative hemostatic intervention* required, as clinically assessed by the treating physician; and/or > 25% drop in hemoglobin compared with baseline.

[a]For the prospective part, the assessment is to include the entire period from the first infusion until 24 hours after the last infusion and include the clinical condition of the subject, laboratory values such as hematocrit and hemoglobin, and any additional hemostatic treatments. The efficacy of only the planned study treatment will be assessed.
*Cryoprecipitate, plasma, recombinant factor VIIa, etc.

Safety variables

- Virus safety
- Vital signs
- Routine clinical laboratory assessment, including coagulation parameters
- AEs, including thromboembolic complications

5.3.3 Major inclusion and exclusion criteria

The major inclusion criteria are: (1) congenital fibrinogen deficiency (afibrinogenemia or severe hypofibrinogenemia) with plasma fibrinogen activity <50 mg/dL and fibrinogen antigen <1.2 times the plasma fibrinogen activity, and (2) presentation with acute bleeding (not requiring surgery).

The major exclusion criteria are: (1) any bleeding disorder other than congenital fibrinogen deficiency, and (2) treatment with a fibrinogen-containing blood product within 2 weeks prior to enrollment or with any coagulation-active drug in the week prior to enrollment.

5.3.4 Status

Study 3001 is an ongoing trial.

5.4 Overview of accelerated approval process as applied to HFC

The development of HFC in the United States is based on the accelerated approval regulations as specified in *Subpart E, Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses [21 CFR 601.41]: Approval based on a surrogate end point or on an effect on a clinical end point other than survival or irreversible morbidity.*

This regulation allows the FDA to approve a BLA based on a clinical trial establishing that a biological product's effect on a surrogate end point is likely to predict clinical benefit. This approval is subject to the requirement that post-marketing work be conducted to verify the product's clinical benefit. The post-marketing study(ies) should be underway prior to BLA approval and conducted with due diligence. The timing for completing post-marketing study(ies) is part of the negotiation process prior to BLA approval and is described in the FDA's BLA approval letter. Additionally, *Subpart G, Postmarketing Studies [21 CFR 601.70]: Annual progress reports of post-marketing studies,* describes the information that the BLA holder will provide to the FDA regarding the status of the post-marketing studies.

The pivotal PK, efficacy, and safety study for HFC, Study 2001, used a biological marker, MCF, as a surrogate for clinical efficacy (control of acute bleeding). Study 3001 is a post-marketing commitment study. The primary objective is to demonstrate hemostatic efficacy in patients treated with HFC compared with a historical control group. This post-marketing study also aims to verify the relationship between MCF and hemostatic efficacy.
For additional information, please refer to **Appendix II.**

6.0 SUPPORTIVE CLINICAL STUDIES IN CONGENITAL DEFICIENCY

Summarized below are the phase I PK study (Study 101) and the virus safety study (Study 402). Also described is the phase IV retrospective study (Study 501), which was conducted to assess the efficacy and safety of HFC in clinical practice.

6.1 Phase I PK study (Study 101)

6.1.1 Design and objectives

This study, conducted in 1993, was designed as a phase I, multicenter, multinational, uncontrolled, prospective, PK, and safety trial of HFC in subjects with congenital fibrinogen deficiency. The primary objective of the study was to determine the PK properties of a single

dose of HFC in 6 patients with congenital afibrinogenemia or severe hypofibrinogenemia. The secondary objective was to obtain safety data on HFC.

The observation period was 10 days from HFC infusion. No fibrinogen-containing drugs were permitted starting 20 days before the study period, and only the single dose of HFC was permitted during the study period; all the subjects had previously been exposed to HFC.

Five of 6 patients completed the study; all received approximately 70 mg/kg body weight of HFC.

6.1.2 Results

The main PK results are presented in **Table 12.**

Table 12. PK results in Study 101

	Basis: Site of Fibrinogen Determinations	
	Investigator's Site	**Manufacturer's Site**
Variable	**Median (Range)**	
Initial half-life (days)	0.22 (0.10–0.24)	0 (0–0.39)
Terminal half-life (days)	3.6 (3.0–5.3)	2.7 (2.5–3.7)
CL[a] (mL/h/kg)	1.65 (0.82–2.55)	0.91 (0.84–1.22)
V_{ss}[a] (mL/kg)	101 (84–139)	89 (81–116)
MRT (days)	2.6 (2.3–4.3)	4.0 (3.3–4.2)
t_{max}[b] (hh:mm)	0:40 (0:29–2:00)	0:40 (0:29–7:50)
Response (mg/dL) / (mg/kg b.w.)	1.45 (1.36–1.91)	1.38 (1.13–1.49)
Recovery (%)	60.0 (53.0–63.8)	54.1 (44.3–61.8)
AUC (days-kg)	2.57 (1.69–4.94)	4.65 (3.05–4.72)

AUC = area under the concentration-time curve; b.w. = body weight; CL = clearance; h = hour; MRT = mean residence time; t_{max} = time to maximal concentration; V_{ss} = volume of distribution at steady state.
[a] Standardized to 1 kg body weight.
[b] Time to maximal fibrinogen concentration.

No conspicuous changes in blood laboratory values (red blood cells, white blood cells, and platelet count; hematocrit and hemoglobin) were detected. Six AEs were reported, none of which were serious. The AEs included dyspnea, elevated temperature, pain at infusion site, headache, and dizziness.

Pathologically prolonged pre-infusion TT and PTT rapidly decreased to normal after infusion, while Quick values (prothrombin time expressed as a percent of normal PT, rather than in seconds) increased to normal **(Table 13)**, thus indicating good efficacy for HFC.

Table 13. Median laboratory values (TT, PTT, Quick)

Time of Determination	TT (sec)	PTT (sec)	Quick (%)
Pre-infusion	120	200	6
1 hour after infusion	20	42	78
4 hours after infusion	20	41	84
1 day after infusion	24	47	68
10 days after infusion	56	74	20

PTT = partial thromboplastin time; Quick = prothrombin time (PT) expressed as a percent of normal PT; sec = seconds; TT = thrombin time.

6.2 Virus safety study (Study 402)

6.2.1 Design and objectives

This study, conducted from June 1985 to June 1987, was a prospective, uncontrolled trial to test the clinical safety of HFC with respect to the transmission risk of HBV; non-A, non-B (NANB) hepatitis virus (as it was called during that time); and HIV-1 in subjects with fibrinogen deficiency.

In this study, only transfusion-naïve subjects (N=4) were chosen, because they acted as their own historical controls. No subjects had a history of hepatitis, and all were negative for HBV sero-markers.

HFC was administered according to clinical need (ie, degree of fibrinogen deficiency and severity of bleeding) adjusted for individual body weight. Single doses ranged from 36 to 67 mg/kg body weight; total dose per subject ranged from 50 mg/kg to 3.3 g/kg. A total of 124.4 g of HFC originating from at least 12 different batches in 64 single infusions were used in the trial. The observation period lasted 9 months.

6.2.2 Results

One subject had been vaccinated against HBV and was thus not evaluable. The 3 other subjects remained free of HBV sero-markers. Likewise all subjects were evaluated for NANB hepatitis but remained free of any signs and symptoms of hepatitis, including liver enzyme abnormalities. All subjects remained negative for anti-HIV-1.

In an amendment to the study, additional data on 2 of the original subjects were presented, and an additional 2 subjects were recruited for a total of 6 subjects. With the additional data, the total amount of HFC used came to 147.4 g from 18 different lots. As before, all tests for the assessed viral sero-markers remained negative and, again, there were no liver enzyme abnormalities. In addition, sero-markers for HAV, HCV, and HIV-2 were also negative. Thus, the study gave no indication of HFC transmission of the blood-borne viruses HAV, HBV, HCV, and HIV-1/2.

Results of this study are also discussed in section 8.4.1.

6.3 Phase IV efficacy study (Study 501)

6.3.1 Design

This was a retrospective, multicenter, open-label study assessing efficacy and safety of fibrinogen replacement in subjects with congenital fibrinogen deficiency.

Major inclusion criteria were subjects of any age suffering from afibrinogenemia, hemostatically relevant hypofibrinogenemia, or dysfibrinogenemia associated with bleeding tendency. Major exclusion criteria were patients with asymptomatic dysfibrinogenemia or dysfibrinogenemia-associated thrombotic events.

For each subject, a treatment interval was documented covering one or more hemorrhagic events, surgical interventions, or prophylactic substitutions. This interval ranged from 1 day to 77 months (median 26.5 months). Duration of treatment for an individual bleeding episode or surgical intervention lasted 1 day to 12 days (median 1 day).

6.3.2 Results

Subjects

Data were collected for 12 subjects (8 males, 4 females) between ages 1 day and 29 years (median 11.5 years) who had congenital fibrinogen deficiency and who were treated with HFC. Eight of these subjects were classified as having afibrinogenemia and 4 hypofibrinogenemia (1 of the latter had combined dysfibrinogenemia/hypofibrinogenemia). No other concomitant illnesses or medications were reported.

Efficacy assessment

Clinical efficacy was evaluated in 26 bleeding events (hemorrhage into muscles or joints, hypermenorrhea, minor or intermediate injury, GI bleeding) and 11 surgical interventions (fracture fixation, pylorotomy, dental surgery, tonsillectomy, dissection of abscess, herniotomy,

fixation of spinal cord). Furthermore, 89 infusions for prophylactic purposes were recorded, 86 of which were given to a single subject. The median single dose in bleeding events or surgical operations was 63.5 mg/kg body weight or 2 g/subject. The median single dose in prophylactic treatment was 76.9 mg/kg body weight or 2 g/subject.

The median response to treatment was an increase of 1.5 ± 0.5 mg/dL in fibrinogen plasma concentration for each milligram of HFC per kilogram body weight administered.

Clinical efficacy of HFC in bleeding episodes and surgical operations was judged to be good in all events except one (pylorotomy), in which efficacy was judged to be moderate. All 89 prophylactic infusions were considered to be efficacious, as no intercurrent bleeding occurred. The hemostatic efficacy of HFC was also excellent, producing normalization or near-normalization of pathologic pre-infusion coagulation parameters, with no bleeding episodes during the study intervals.

Safety assessment

Safety results are presented in section 8.0.

7.0 SUMMARY OF EFFICACY

The clinical efficacy of HFC in the treatment of congenital fibrinogen deficiency has been assessed in 3 studies to date (Studies 2001, 501, and 1221). Congenital fibrinogen deficiency is so rare that a study design incorporating efficacy end points poses a considerable challenge. The efficacy assessments in these studies, summarized in **Table 14**, include physicians' clinical judgment, coagulation parameters, and MCF, an index of clot stability. In all 3 studies, HFC has consistently yielded positive results for each of these efficacy measures.

Table 14. Summary of clinical efficacy

Study	Population	Assessment	Key Results
2001	15 subjects with congenital afibrinogenemia, treated with HFC	MCF	Highly significant (p<0.0001) increase in mean MCF from baseline
501	12 subjects with congenital afibrinogenemia or hypofibrinogenemia, treated with HFC	Plasma fibrinogen	Levels increased by median of 1.5 ± 0.5 mg/dL per mg/kg b.w. of HFC
		Clinical assessment	Efficacy good for all bleeding or surgical events (except 1 pylorotomy judged as moderate); all prophylactic treatments were efficacious (no intercurrent bleeding)
1221	100 subjects with congenital fibrinogen deficiency (517 bleeding episodes), treated with fibrinogen concentrates (primarily HFC), cryoprecipitate, or other modality	Clinical assessment	Fibrinogen concentrates used slightly more often for fibrinogen replacement Fibrinogen concentrates and cryoprecipitate both considered efficacious for restoration of hemostasis in >90% of events

b.w. = body weight; HFC = human fibrinogen concentrate; MCF = maximum clot firmness.

8.0 SUMMARY OF SAFETY

The congenital deficiency (CD) clinical safety database for HFC is derived from the standardized collection of safety data prospectively collected from the pivotal PK and safety study (Study 2001) and the 3 supporting CD clinical studies (Studies 101, 402, and 501). These 4 CD studies report safety following 244 doses of HFC in 39 subjects.

The acquired deficiency (AD) safety database reports safety following 283 doses of HFC in 92 subjects enrolled in the AD, post-marketing, observational case collection study, which is also referred to as the "Clinical Observational Monitoring Project," or COMP (Study 7D-501).

The total clinical trial safety database reflects safety following 527 doses of HFC in 131 subjects.

Additional safety data are available but difficult to interpret.

- In the retrospective physicians survey (Study 1221), physicians were not explicitly asked to report on safety, but some safety data are contained in reports from 100 participants.
- An observational case collection was conducted from 1984 to 1986 that included at least 37 CD and AD patients. This case collection was conducted by a German marketing organization. The safety information is not complete, no study report or summary tables are available, and data were not collected or documented in compliance with any standards. Most of the 37 cases were from patients with AD and it is certain that 4 cases were from patients with CD. There were a total of 7 AEs; no event was reported to be related to HFC. All deaths occurred in AD cases and are summarized separately in **Appendix IV**.

In addition, 22 years of post-marketing data confirm the safety of HFC demonstrated in the clinical trials.

8.1 Non-serious adverse-event summary of clinical studies

Non-serious AEs reported in Study 2001 included epistaxis, flare up of gastroesophageal reflux disease, headache, and pain. In Study 101, 6 mild-to-moderate AEs were reported in 4 subjects, including dyspnea, elevated temperature, pain at infusion site, headache, nausea, and dizziness. In AD study 7D-501, there were 2 reported fever events in 2 subjects of mild-to-moderate severity. In this observational trial, conducted from 1991 to 1994, only treatment-emergent events that were considered to be a side effect of treatment were reported. No AE or serious AE

(SAE) in the clinical trials led to permanent discontinuation of treatment. **Table 15** presents a summary of non-serious AEs in the HFC clinical trials.

Table 15. Summary of non-serious AEs in HFC clinical trials

Occurrence of AE	CD Study 2001 (N=15; 15 doses)	CD Study 101 (N=6; 6 doses)	CD Study 501 (N=12; 151 doses)	CD Study 402 (N=6[a]; 72 doses)	AD Study 7D-501 (N=92; 283 doses)
Subjects with ≥1 AE	2	4	0	0	2
Subjects with ≥1 possibly treatment-related AE	0	2	NA[b]	0	2

AD = acquired deficiency; AE = adverse event; CD = congenital deficiency; HFC = human fibrinogen concentrate.
[a] Four subjects analyzed in original study report; 2 subjects added to analysis by report amendment.
[b] No information on causal relation of AE to study drug in clinical study report.

8.2 Serious adverse events in clinical studies

Two SAEs were reported in the clinical trials, both of which occurred in the prophylactic CD study 501. In this study, 12 subjects received 151 doses of HFC over a period of 1 day to 77 months (median 26.5 months).

There was one reported event of anaphylaxis in Study 501 following the 56th dose in a 7-year-old female subject receiving prophylaxis for congenital fibrinogen deficiency. This event did not lead to discontinuation of HFC treatment. Subsequent doses (doses 57 to 87) were tolerated without event.

An SAE that occurred outside the documented study period was judged as possibly related to HFC. Following internal fixation surgery of a fractured femur, the 25-year-old subject was treated with a total of 6 doses of HFC despite having a known DVT two days prior to the 6th (last) dose. Nineteen days after the last dose, the subject was diagnosed with an angiography-confirmed pulmonary embolism.

In the post-marketing, observational case collection (Study 7D-501) conducted in Germany from 1991 to 1994, all 92 enrolled patients had acquired fibrinogen deficiency (not congenital

fibrinogen deficiency, which is the indication currently being sought). This population was critically ill: The majority had pre-existing serious underlying conditions that resulted in an acute acquired fibrinogen deficiency, including disseminated intravascular coagulation (DIC) (28%) and shock (32%), conditions with a very high mortality rate. Use and dose of HFC were guided by physicians' assessments of therapeutic necessity; there was no specific treatment study protocol. The treatment period for HFC was 1–12 days (mean 2.6 days).

During the course of this 35-month observational study, 20 patients died. No death was judged as related to HFC treatment nor was consistent with any known or suspected effect of fibrinogen. All deaths had an investigator-provided explanation (the majority due to the underlying acute disease). All deaths were reported but were not recorded as AEs. These *events* with fatal outcome did not meet the definition of a suspected serious adverse *reaction*, which, as applicable, would have been subject to expedited reporting to concerned regulatory authorities. **Appendix IV** contains the narratives and a summary of the death events **(Table 21).**

8.3 Post-marketing safety

Post-marketing surveillance supports the favorable safety profile of HFC and shows a pattern of suspected adverse drug reactions (ADRs) consistent with the AEs observed in HFC clinical studies.

HFC was introduced into the European market in 1986 for patients with both congenital and acquired fibrinogen deficiency. Since then, it has been used in several European countries and other regions outside the United States to treat and prevent bleeding in patients with congenital afibrinogenemia, hypofibrinogenemia, or certain types of dysfibrinogenemia (ie, those with bleeding tendency), or acquired hypofibrinogenemia.

Assessment of post-marketing data was based on data collected by a post-marketing surveillance system that captured spontaneous reports, reports from the scientific literature, and reports from unsponsored studies of suspected ADRs. The number of ADR reports was compared with the

number of estimated single standard doses. The estimated dose per patient ranged from 1 to 8 g, depending on the degree of bleeding.

Between January 1, 1986, and October 31, 2008, a total of 1,063,691 g of HFC were distributed. A total of 49 spontaneous reports of ADRs from 49 patients was received from the whole market, 46 (94%) of which were expected, based on the safety profile of HFC, and 3 (6%) of which were unexpected. This corresponds to 1 report for every 21,708 one-gram applications and 1 report for every 2,713 eight-gram applications, respectively.

Three fatal case reports were received. Case summaries of the deaths are provided in **Appendix III.** In these cases, the patients died because of an underlying disease: one was an adult female with cerebral bleeding (Case PVD2) and the other (Case PVD3) was a newborn who had undergone surgery for a congenital heart defect and had been placed on extracorporeal membrane oxygenation (ECMO). In the third case, an 81-year-old patient with multiple cardiac disorders developed suspected anaphylactic shock during surgery when various other medications were administered (Case PVD1). These other medications had a higher allergic potential than HFC. The reported cause of death was cardiac failure, not the hypersensitivity reaction.

As shown in **Table 16**, expected ADRs included allergic or anaphylactic reactions, thromboembolic events, suspected transmission of infectious disease, and lack of treatment effect. Of the 46 expected ADRs reported from the whole market, 24 were assessed by the sponsor as possibly related to HFC administration; 7 had insufficient data to support a causal determination; and 13 were assessed by the sponsor as unrelated to HFC.

Table 16. Overview of expected and unexpected ADRs, number of cases, indications, and causality

ADRs	Number of Reported Cases	HFC Indication	Sponsor Assessment of Causality
Expected			
Allergic/allergoid/ anaphylactic/anaphylactoid reaction (including generalized reactions such as chills, fever, nausea, vomiting)	20[a]	CD afib 12; CD hypofib 3; AD 2; Unknown 3	16 possibly related; 3 insufficient data; 1 unlikely
Thromboembolic events	9[a]	CD afib 7; CD hypofib 1; AD 1	8 possibly related; 1 insufficient data
Suspected transmission of an infectious disease	14[a]	CD dysfib 1; CD afib 1; AD 12	13 unrelated; 1 insufficient data
Lack of effect[b]	3	All CD afib	1 unlikely; 2 insufficient data
Unexpected			
Transient bone pain/chills	1	CD afib	Possibly related
Leucocytosis	1	Unknown	Unrelated
Lung infiltration	1	Unknown	Unrelated

AD = acquired deficiency; ADR = adverse drug reaction; afib = afibrinogenemia; CD = congenital deficiency; dysfib = dysfibrogenemia; HFC = human fibrinogen concentrate; hypofib = hypofibrinogenemia.
[a] Case summaries provided in **Appendix III**; one case is a duplicate of a clinical-trial SAE.
[b] In general, lack of effect is considered a listed ADR although it is never explicitly stated in the safety information.

The three cases of unexpected ADRs were as follows:

- Bone pain and chills that subsided within 24 hours.
- Patient presented with fever and mild leucocytosis; after treatment with HFC for an unrecorded indication, the leucocytosis increased.
- Following HFC administration (in addition to packed red blood cells [PRBCs], plasma, and platelets), patient developed lung infiltration, which was attributed to volume overload.

In summary, post-marketing surveillance over 22 years, during which time approximately 1 million grams of HFC were distributed, demonstrated only 49 ADRs. The most common of these were allergic/anaphylactoid reactions. There were no confirmed cases of virus transmission by HFC and also no reports of suspected inhibitory antibodies to fibrinogen.

8.4 Adverse events/laboratory results of special interest

8.4.1 Virus safety

The results of virus validation studies of the manufacturing process, clinical trials, and post-marketing studies consistently demonstrate the safety of HFC with regard to virus transmission. No evidence appears in any of these reports indicating virus transmission caused by HFC therapy.

Transmission of viral infections was not detected in the 21 subjects enrolled in the two CD clinical studies in which virus safety was evaluated (Studies 2001 and 402).

Virus marker data were available for all 15 subjects in Study 2001, as planned in the protocol. None of the subjects tested negative at pre-infusion and positive at a follow-up visit for any of the virus markers. None of the subjects who were missing pre-infusion data were seropositive at the follow-up measurement. One subject was positive for HAV antibodies at baseline but negative at Day 45. Another subject had an equivocal HCV-PCR finding at Day 45, but subsequent testing at another laboratory established the results as negative.

In Study 402, two subjects were immunized against HBV during the follow-up, resulting in detectable hepatitis B virus surface antibodies (anti-HBs). However, the subjects remained negative for hepatitis B virus surface antigen (HBsAg) and anti-hepatitis B virus core antigen (anti-HBc). The remaining 4 subjects were negative for seromarkers of HBV throughout the study, with the exception of one isolated transient positive anti-HBc result in one subject; subsequent testing confirmed the absence of anti-HBc antibodies in this subject. There was no indication of an infection with HCV or HIV-1 in any of the 6 subjects in this study.

Over 22 years, there were 14 post-marketing reports of suspected virus transmission; one report had insufficient data, and only two cases were in patients with a congenital fibrinogen deficiency **(Table 17)**.

Table 17. Post-marketing suspicion of virus transmission cases (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 1st 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) *(HCV neg in 05/96)*	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

Case No.	Age (yrs)	Indication for Treatment	Time Between HFC Dose and Event	Lab Event (Year)	Co-suspect Plasma/Blood Products/Events
V14	44	AD, DIC/multiple trauma	25 to 37 mos from single dose in 11/01	HCV+ (2004)	PRBCs, platelets, ATIII

+ = positive; AD = acquired deficiency; ALL = acute lymphoblastic leukemia; ATIII = antithrombin III; CD = congenital deficiency; DIC = disseminated intravascular coagulation; dx = diagnosed; dysfib = dysfibrinogenemia; HBcAg = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; hep B = hepatitis B; hep C = hepatitis C; mos = months; NA = not available; neg = negative; PCC = prothrombin complex concentrate; PRBCs = packed red blood cells; U = units; yrs = years.

In the 13 reports with sufficient data, a causal relation between HFC and virus transmission could not be concluded due to confounding co-suspect products and/or negative PCR test results for the concerned batches as follows:

- Concomitant administration of non–virus-inactivated products or other blood products (12 reports)
- Time point of infection unclear or does not match HFC treatment dates (5 reports)
- Batches manufactured from HCV-PCR negative-tested source material (2 reports)
- Batches retrospectively found to be HCV-PCR negative (3 reports)

8.4.2 Thrombotic risk

8.4.2.1 Markers of activation in the coagulation pathway

Fibrinogen is not a procoagulant; rather, it is an inactive substrate. HFC administration replaces fibrinogen in patients with severe fibrinogen deficiency. When HFC is administered, it acts as a substrate for thrombin, which cleaves fibrinogen to form fibrin, and ultimately, a cross-linked fibrin clot. As part of the body's normal response to clot formation, plasmin cleaves the cross-linked fibrin to generate D-dimer; therefore, it is expected that D-dimer levels are elevated in response to the size of the clot and duration of fibrinogen replacement therapy. Potential indicators of a hypercoagulable state are the thrombin-antithrombin III complex (TAT) and fibrin fragments F1+2 (F1+2).

Results of the laboratory assessment of coagulation activation (thrombin generation) from the 6-subject CD Study 101 are shown in **Table 18.** Fibrinogen levels were markedly lower than the lower limit of normal at all time points. Abnormal pre-infusion TT, PTT, and Quick (prothrombin time expressed as a percent of normal PT, rather than in seconds) values were rapidly normalized or markedly improved post-infusion of HFC. All subjects had slight increases in D-dimer, F1+2, or TAT values, which may have indicated a mild, transient activation of fibrinogen and subsequent fibrinolysis. All subjects had increased D-dimers as expected due to reconstitution or improved hemostasis in these patients with afibrinogenemia or hypofibrinogenemia. However, F1+2 and TAT levels were minimally and only transiently (less than 1 day) elevated, suggesting there was no increased thrombotic risk.

Table 18. Markers of coagulation activation in CD Study 101

Variable (unit)	Normal Range	Pre-infusion (Median)	Post-infusion (Median)			
			1 hour	4 hours	1 day	10 days
Fibrinogen (mg/dL)	180–350	8	95	79	60	9
TT (sec)	13–16	120	20	20	24	56
PTT (sec)	<45	200	42	41	47	74
Quick (% of normal PT)	70–120	6	78	84	68	20
D-dimer (ng/mL)	<500	5	40	63	53	20
F1+2 (nmol/L)	0.4–1.1	1.1	1.1	2.3	1.4	1.2
TAT (μg/L)	<4	3.5	5	5.1	2.6	2.6

CD = congenital deficiency; F1+2 = fibrin fragment F1+2; PT = prothrombin time; PTT = partial thromboplastin time; Quick value = prothrombin time defined as % of normal, not in seconds: TT = thrombin time; TAT = thrombin-antithrombin III complex.

During the 15-subject, 2001 CD study, in which 14 subjects were evaluated for PK parameters, some fluctuation in laboratory indicators of coagulation activation was observed but not considered by the investigators to be clinically relevant. All but 1 subject had either normal values at pre-infusion and at all time points thereafter or high levels pre-infusion that normalized thereafter for the F1+2 coagulation parameter.

8.4.2.2 Thromboembolic events

Overall, the occurrence of thromboembolic events in HFC clinical trials and post-marketing surveillance has been rare. In the clinical trials of HFC, where 131 subjects received a total of 527 doses, only one thromboembolic event was reported in a high-risk subject following femur fracture surgery.

A total of 9 reports of thromboembolic events after distribution of approximately 1 million grams of HFC have been received throughout post-marketing surveillance. Of note, all but one patient had a congenital fibrinogen deficiency, which is associated with a higher risk of thrombotic complications independent of HFC treatment. **Table 19** summarizes these reports.

Table 19. Post-marketing thromboembolic events (1986–2008)

Case No.	Age (yrs)	Indication for Treatment	Major Symptoms/ Underlying Conditions *(Comment)*	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 brachioceph -alicus	Activated FVII, activated PCC
TE2	44	CD afib	*(Possible antibody interference with heparin)*	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 of 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 after iatrogenic	NA	Massive proximal DVT/	-

Case No.	Age (yrs)	Indication for Treatment	Major Symptoms/ Underlying Conditions *(Comment)*	Dosing of HFC	Time Between Last HFC Dose and Event	Event[a]	Co-suspect Products
				arterial injury (8-g single doses)		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 hypofib	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 wks)	3 wks	Pulmonary embolus/ recovered	-

AD = acquired deficiency; afib = afibrinogenemia; AML = acute myeloid leukemia; CD = congenital deficiency; CVA = cerebral vascular accident; DVT = deep vein thrombosis; FVII = factor VII; hrs = hours; hx = history; hypofib = hypofibrinogenemia; ICH = intracerebral hemorrhage; i.v. = intravenous; NA = not available; PCC = prothrombin complex concentrate; SC = subclavian; SDH = subdural hematoma; tx = treatment; wks = weeks; yrs = years. [a] All cases recovered except TE1 (subject died from life-threatening bleeding) and TE4 (subject's vision did not improve).

In most of these cases, additional risk factors provided alternative explanations for the thromboembolic events:

- Concomitant treatment with other coagulation factor products (such as prothrombin complex concentrate [PCC], platelets, recombinant activated factor VII) or other drugs that may increase risk (such as aprotinin) (3 cases), and/or
- A higher risk of thrombosis due to baseline congenital fibrinogen abnormalities. One of the potential complications of this disease includes an increased risk of paradoxical thrombotic complications [Lak 1999, Peyvandi 2006] (8 cases).

Appendix III presents the narratives for the 9 post-marketing case reports of thromboembolic events.

In the retrospective CD survey of physicians (Study 1221), which was not designed to collect safety events, 2 out of 44 HFC-treated patients were reported to have had a thromboembolic event. One patient, treated with 63 mg/kg of HFC every 2 weeks, developed a stroke. The dose

was decreased to every 3 weeks without a further thrombotic event; however, the patient developed an intracranial hemorrhage (ICH) on the lower dose. A second patient, treated with 61 mg/kg weekly, developed occlusive arterial disease in the leg, and the dose was reduced to 30 mg/kg twice a week. In addition, one patient out of 43 receiving cryoprecipitate was reported to have experienced "thrombosis."

8.4.3 Hypersensitivity risk

Because HFC is a plasma-derived product, hypersensitivity reactions might be expected. These events, however, were uncommon. In the clinical trials (Study 501) as previously summarized, there was one reported event of anaphylaxis following the 56th dose in a subject receiving prophylaxis for congenital fibrinogen deficiency. Subsequent doses (doses 57 to 87) were tolerated without event.

The majority of the 20 possible hypersensitivity reactions that were reported in 22 years of post-marketing surveillance were mild and resolved after treatment with antihistamines or glucocorticoids **(Table 20)**. **Appendix III** provides the narratives for these cases.

Table 20. Post-marketing reports of possible hypersensitivity reactions

Symptoms	Numbers of Reports
Chills/fever	10
Rash/swelling	2
Circulatory reactions (hypotension, tachycardia) without reaching diagnostic criteria for anaphylaxis[a]	1
Met diagnostic criteria for anaphylaxis	6
Not properly described	1
Total	**20**

[a] Sampson HA, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 117, no. 2 (2006):391-7.

8.5 Safety conclusions

The clinical studies of HFC establish a favorable safety profile. Analyses of AEs following HFC administration reveal no safety issues of concern; AEs occurring during clinical trials were few and generally mild; and no AEs led to discontinuation of HFC treatment. Post-marketing surveillance (with approximately 1 million grams of HFC distributed) likewise supports the favorable safety profile of HFC, demonstrating a pattern of ADRs consistent with the AEs observed in clinical trials.

9.0 SUMMARY OF RISK VERSUS BENEFIT

9.1 Benefits

In addition to the 22 years of clinical experience with HFC (including published literature) in treating or preventing bleeding in patients with fibrinogen deficiency, the proven ability of HFC to consistently raise plasma fibrinogen to hemostatic levels and increase MCF supports its benefits. There have only been 3 spontaneous reports of lack of efficacy (following distribution of approximately 1 million grams of HFC); all 3 cases occurred in patients with afibrinogenemia.

9.2 Thrombotic risk

In clinical studies of HFC, only one thromboembolic event following surgery for femur fracture was reported, and laboratory measures of coagulation activation in subjects before and after HFC administration (Studies 101 and 2001) revealed no clinically relevant changes. Post-marketing surveillance of HFC has yielded 9 reports of thromboembolic events, all but one occurring in congenital fibrinogen deficiency patients. Most subjects had additional risk factors for thrombosis, including the increased thrombotic risk associated with congenital fibrinogen deficiencies, rendering the relationship with HFC therapy unclear. The safety data suggest thrombotic complications are associated with risks inherent to the congenital fibrinogen deficiencies and are not due to fibrinogen replacement therapy.

Assessing thrombotic risk for HFC administration is complicated by the fact that thrombosis may occur spontaneously in this population. Patients with afibrinogenemia and other forms of congenital fibrinogen deficiency experience a greater degree of arterial and venous thrombosis, with or without use of fibrinogen replacement therapy [Girolami 2006, Lak 1999, Mosesson 2003, Peyvandi 2006, Roqué 2004]. It has been demonstrated that thrombin levels are elevated in afibrinogenemia, thus leading to platelet-mediated thrombosis [Dupuy 2001].

The risk of thrombotic complications is anticipated to be lower with a purified concentrate such as HFC, which is simply a coagulation factor replacement, than with cryoprecipitate (the current US standard of care) that contains procoagulants, such as factor VIII and vWF. However, insufficient data exist to prove this clinically. Therefore, the risks of thrombosis need to be weighed carefully against the risks of fatal bleeding in patients with congenital fibrinogen deficiencies [Henselmans 1999].

9.3 Pathogen transmission risk

Since blood and blood components (plasma, cryoprecipitate) are not treated for virus and other pathogen inactivation or removal, the risk of transfusion-transmitted diseases remains. In contrast, HFC is treated for virus and other pathogen inactivation and removal, undergoing pasteurization and other processing steps that reduce the risk of transfusion-transmitted diseases [Ofosu 2008]. In addition, for all plasma products in the United States, rigorous measures are taken to minimize or eliminate known risks at collection of the plasma to be used in the manufacture of HFC. The clinical and post-marketing experience with HFC, following distribution of approximately 1 million grams over 22 years, has indicated no evidence of virus or other pathogen transmission with this product.

9.4 Hypersensitivity risk

The administration of unnecessary plasma proteins in plasma and cryoprecipitate always poses some risk of allergic reactions (20%–30% [McVerry 1979]) or anaphylactic reactions. A concentrate, such as HFC, reduces the risk significantly by reducing the amount of potential

proteins that can cause a reaction. The 22-year-old post-marketing database includes only 20 reports of hypersensitivity reactions in approximately 1 million grams of HFC administered, a markedly lower rate than that reported with plasma or cryoprecipitate.

9.5 Overall

HFC has been proven to reliably and consistently raise plasma fibrinogen to hemostatic levels. These results, paired with over 22 years of clinical experience and distribution of approximately 1 million grams of HFC, in treating or preventing bleeding in patients with fibrinogen deficiency support the benefits of HFC. There are rare potential risks of hypersensitivity and thrombosis, of which medical professionals and patients should be aware. However, fatal or disabling bleeding is a real risk in patients with congenital fibrinogen deficiency who are not treated. Furthermore, the potential risks are reduced by administration of a concentrate with a defined composition compared with whole plasma or cryoprecipitate. Overall, the benefit-risk profile favors HFC therapy in this population.

10.0 CONCLUSION

HFC (Riastap™), when approved for use in the United States, will provide a safe and effective product that is an optimized treatment for patients with the rare condition of congenital fibrinogen deficiency. The virus safety of this product is achieved through rigorous control of plasma collection, release of plasma pools for fractionation, and a multi-step manufacturing process, resulting in an appropriate margin of virus safety.

HFC has distinct advantages over the currently available treatments in the United States, plasma and cryoprecipitate:

- Improved precision of therapeutic effect, infusing only fibrinogen to correct fibrinogen deficiency
- Reduced time in preparation/administration of infusion, an advantage for patient safety
- Purified and concentrated lyophilized protein that is easily reconstituted in minutes

- Concentrated fibrinogen allows for low infusion volume and quick intervention
- Demonstrated ability to effectively raise fibrinogen levels to within target levels
- Safe and well tolerated with a low risk of AEs
- Virally inactivated to reduce risk of exposure to infectious agents
- Room-temperature storage and extended shelf life afford easy storage and access when needed
- Eliminates inventory constraints related to plasma component therapy

CSL Behring, a company that has a history of providing safe and efficacious plasma products, has produced and distributed approximately 1 million grams of HFC in over 22 years for the treatment of fibrinogen deficiency. Because of the rarity of congenital fibrinogen deficiency, adequately powered controlled studies utilizing HFC are not possible. However, the clinical program we have undertaken for this approval, as well as previous studies and long-term post-marketing data, support both the efficacy and safety of HFC for the treatment of fibrinogen deficiency.

HFC has been shown to reliably raise plasma fibrinogen concentrations to target levels and to increase MCF, a surrogate measure of hemostasis. The MCF [± SD] at 1 hour post infusion was 10.3 ± 2.7 mm for the 13 subjects who had complete data; at baseline MCF was 0 for all subjects (Note: The normal MCF range for plasma was 14 - 30 mm). These findings will be confirmed in a phase IIIb post-marketing commitment study (Study 3001). In a retrospective, international survey of physicians (Study 1221), the use of fibrinogen concentrates was judged to be effective for treating bleeding events.

HFC is well tolerated. In the pivotal PK and safety study (Study 2001), only 2 subjects had AEs, which were mild and considered to be unrelated to treatment. Clinical studies including a virus safety trial with a 1-year follow-up showed no viral transmission. Furthermore, post-marketing safety data, collected since 1986 in countries where HFC is approved, confirm virus safety, with no proven cases of viral transmission. Risks of thromboembolic events exist due to the deficiency itself, and risks of hypersensitivity reactions exist with the infusion of any blood

product (including cyroprecipitate, the current US standard of care). However, post-marketing surveillance shows that the incidence of these events and reactions in patients treated with HFC is low, and, because of confounding factors, a causal relationship with HFC has neither been proven nor excluded. The real risk of fatal or disabling bleeding without treatment must always be weighed against these identified potential risks of treatment.

The Medical and Scientific Advisory Council of the National Hemophilia Foundation has emphasized the importance of viral safety for blood factor concentrates, encouraging blood-plasma manufacturers to produce factor concentrate therapies for rare disorders. The FDA has supported this recommendation by calling for new concepts in clinical trial design and clinical end points to encourage the development of innovative therapies. HFC is an answer to these recommendations and addresses a significant unmet medical need for patients with congenital fibrinogen deficiency in the United States.

HFC is an effective and well-tolerated treatment for congenital fibrinogen deficiency. When approved, it will improve the care of patients with this rare bleeding disorder.

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12.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Acquired deficiency
ADR	Adverse drug reaction
AE	Adverse event
Afib	Afibrinogenemia
ALL	Acute lymphoblastic leukemia
AMI	Acute myocardial infarction
AML	Acute myeloid leukemia
Anti-HBs	Hepatitis B virus surface antibodies
ATIII	Antithrombin III
AUC	Area under the concentration-time curve
B19V	Human parvovirus B19
BLA	Biologics License Application
BMI	Body mass index
BVDV	Bovine viral diarrhea virus
b.w.	Body weight
CBER	Center for Biologics Evaluation and Research
CD	Congenital deficiency
CD afib	Congenital afibrinogenemia
CL	Clearance
C_{max}	Maximum concentration within 4 hours
COMP	Clinical observational monitoring project
COPD	Chronic obstructive pulmonary disease
CPV	Canine parvovirus
CVA	Cerebral vascular accident
DIC	Disseminated intravascular coagulation
dL	Deciliter
DVT	Deep vein thrombosis
dx	Diagnosed
Dysfib	Dysfibrinogenemia
ELISA	Enzyme-linked immunosorbent assay
ECMO	Extracorporeal membrane oxygenation
F1+2	Fibrin fragment F1+2
FVII	Factor VII
FDA	Food and Drug Administration
FDAMA	FDA Modernization Act
g	Gram
GCP	Good Clinical Practice
GI	Gastrointestinal
h	Hours
HAV	Hepatitis A virus
HBcAg	Hepatitis B virus core antigen
HBeAg	Hepatitis B virus envelope antigen

Abbreviation	Definition
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hep B	Hepatitis B
Hep C	Hepatitis C
HFC	Human fibrinogen concentrate (generic name for Riastap™)
HIV-1/2	Human immunodeficiency virus-1/2
HSV-1	Herpes simplex virus-1
hx	History
Hypofib	Hypofibrinogenemia
i.a.	Intra-arterial
i.c.	Intracutaneous
ICH	International Conference on Harmonization
ICH	Intracerebral hemorrhage
IND	Investigational New Drug
inf.	Infusion
ITT	Intention-to-treat
IU	International units
i.v.	Intravenous
IVR	*In vivo* recovery
kg	Kilogram
L	Liter
LMWH	Low-molecular-weight heparin
MASAC	Medical and Scientific Advisory Council
MCF	Maximum clot firmness
mg	Milligram
mL	Milliliter
MRT	Mean residence time
n.d.	Not done
NA	Not available
NANB	Non-A, non-B
NAT	Nucleic Acid Testing
NHF	National Hemophilia Foundation
OBRR	Office of Blood Research and Review
OMCL	Official Medicine Control Laboratory
PCC	Prothrombin complex concentrate
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PP	Per-protocol
PRBCs	Packed red blood cells
PRV	Pseudorabies virus
PT	Prothrombin time
PTT	Partial thromboplastin time
p.v.	Paravenous

Abbreviation	Definition
Q25	25% quartile
Q75	75% quartile
SAE	Serious adverse event
SC	Subclavian
s.c.	Subcutaneous
SD	Standard deviation
SDH	Subdural hematoma
sec	Seconds
$t_{1/2}$	Terminal elimination half-life
TACO	Transfusion associated circulatory overload
TAT	Thrombin-antithrombin III complex
t_{max}	Time to maximal concentration
TRALI	Transfusion related acute lung injury
TT	Thrombin time
U	Unit(s)
US	United States
V_{ss}	Volume of distribution at steady state
vWF	von Willebrand factor
wks	Weeks
WNV	West Nile virus
y.o.	Year old
yrs	Years

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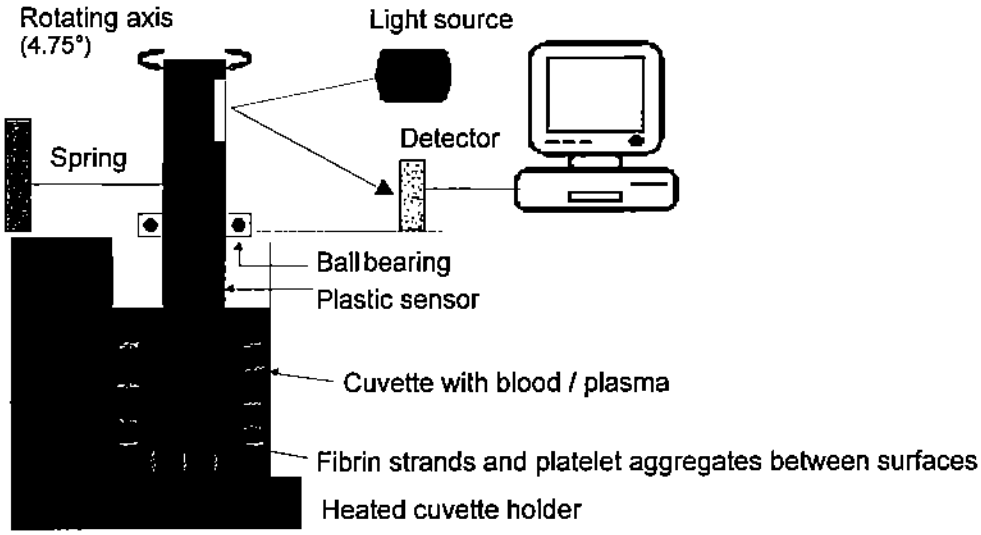
15.0 APPENDICES

Appendix I. ROTEM® and MCF

Rotation thromboelastometry (ROTEM®) is a viscoelastic test. The basic principle is measurement of the properties of a clot formed between a pin placed in a blood or plasma sample and the wall of a container **(Figure 4)**.

Figure 4. Principle of ROTEM®



- A disposable pin is attached to the tip of an axis, which can rotate, and inserted into a stationary disposable cuvette.
- A blood or plasma sample and coagulation activators are added to the cuvette.
- The axis rotates back and forth and is connected to a spring, which allows measurement of the elasticity of the clot as it forms and lyses within the cuvette. The distance between the wall of the cuvette and the pin is 1 mm.
- The position of the axis is detected by reflection of light on a small mirror on the axis.
- A detector records the axis rotation over time and this rotation is translated into a graph or thromboelastogram.

A thromboelastogram **(Figure 5)** illustrates clotting and clot firmness during the entire coagulation process. The ROTEM® parameters are as follows:

- *Clotting time (sec):* initiation of clotting, thrombin formation, start of clot polymerization
- *Clot formation time (sec)*: fibrin polymerization, clot stabilization with platelets and factor XIII
- *Maximum clot firmness (mm)*: increasing stabilization of the clot by polymerized fibrin, platelets, and factor XIII
- *Maximum lysis (% of MCF):* stability of the clot (<15%) or fibrinolysis (>15% within 1 hour)

Figure 5. ROTEM® thromboelastogram: typical reaction curve

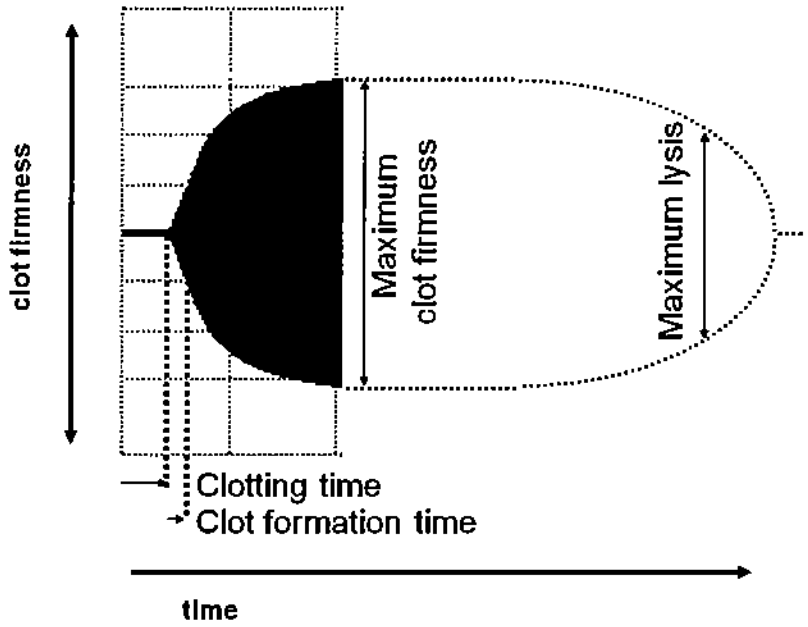
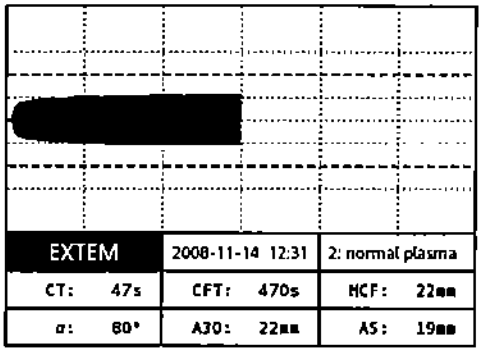


Figure 6. Thromboelastograms from normal and fibrinogen-deficient samples

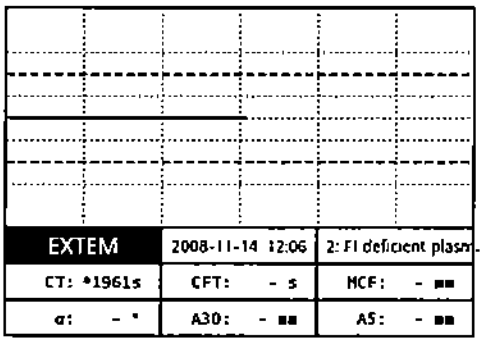
Definition exTEM: exTEM contains an optimized concentration of thromboplastin that is used for a mild, standardized extrinsic activation of coagulation system.

PLASMA

Normal healthy subject



Fibrinogen deficiency



Advantages of ROTEM® compared with TEG®

- The test is not susceptible to mechanical vibrations or shocks to the equipment [Simioni 2008].
- It uses an electronic pipette that increases reproducibility [Simioni 2008].
- Results are available within minutes [ROTEM® 2008].
- Coagulation can be triggered using different activators, making it possible to evaluate different activation pathways [Simioni 2008].
- Reagents for 5 standard assays are provided from the manufacturer, including those for the assessment of the role of fibrinogen in clot formation.
- Only a low volume of blood or plasma (300 μL) is needed.
- The test is less affected by pre-analytical conditions.

Appendix II. Overview of accelerated approval process

Subpart H of 21 CFR 314.500 (Code of Federal Regulations), known as the Accelerated Approval provisions of the FDA regulations, codified the approval process for new drugs or biologicals intended for the treatment of serious and life-threatening illnesses. This specifically addresses the need to develop treatments that would provide meaningful therapeutic benefit over existing treatments and treatments for which the proposed clinical benefit might not be detectable in traditional clinical trials of reasonable duration or size.

In the case of a rare disease with a low rate of the event(s) leading to the primary end point of a clinically meaningful benefit, a traditional clinical trial that is designed to detect the difference between a new therapy and a placebo, or the difference between a new therapy and an active comparator that represents the current standard of care, could require the enrollment of large numbers of subjects and last many years. When it is not feasible to base the trial outcome on an end point of clinically meaningful benefit, a surrogate end point might, under certain circumstances, be employed instead.

In a clinical trial, a clinical end point is the measure of an outcome that has clinically meaningful benefit in the sense that it measures directly how a subject feels, functions, or survives. For example, in the investigation of a cancer treatment, the number of deaths over a specified period of time is a clinical end point; in an investigation of a treatment for age-related macular degeneration, loss of vision is a clinical end point.

A surrogate end point is a laboratory test or physical sign that substitutes for a clinical end point. A surrogate end point demonstrates that some biological marker has a plausible relationship to a clinical end point, which shall be referred to in what follows as the target clinical end point.

A biological marker is a measurable manifestation of a process or entity occurring or existing at the molecular, cellular, or organ level or at the level of an organism itself (eg, the number of sodium ions present in plasma, the presence of B-cells in the blood, the production of certain enzymes in the liver, or a person's body temperature).

In order for a particular biological marker to serve as a surrogate for a target clinical end point, two essential aspects of the biological marker must be demonstrated:

1. A plausible biological connection exists between the biological marker and the target clinical end point;
2. Treatment-associated change in the biological marker tracks in understandable and meaningful fashion with the treatment-associated change in the target clinical end point.

When these two conditions are met, the biological marker is referred to as a surrogate end point for the target clinical end point. Additionally, when one is able to demonstrate in several randomized clinical trials (with the same target clinical end point and in which the surrogate end point is also observed) that: 1) a strong association between the treatment-related change in the surrogate end point and the treatment-related change in the target clinical end point is observed; 2) this association is maintained in trials in different populations of subjects, using different

therapeutic agents; and 3) this association is maintained in trials that focus on different diseases or disease states, then one may claim that the surrogate end point has been *validated* for the disease setting and the class of therapeutic agents studied.

In his article titled "Surrogate end points and FDA's accelerated approval process," Thomas R. Fleming (2005) posits an end point hierarchy for outcome measures in clinical trials:

Level 1: a true clinical-efficacy measure; Level 2: a validated surrogate end point (for a specific disease setting and class of interventions); Level 3: a non-validated surrogate end point, yet one established to be "reasonably likely to predict clinical benefit" (for a specific disease setting and class of interventions); and Level 4: a correlate that is a measure of biological activity but that has not been established to be at a higher level.

Typically, FDA regulations require that the primary end point of a pivotal clinical trial for marketing approval of a therapeutic agent must be at Level 1 or Level 2 in Fleming's hierarchy and may be at Level 2 only in, "those cases in which an effect on a clinical outcome … cannot be detected in a practically performable clinical trial" (Katz 2004).

However, in 1997, the United States Congress, as part of the FDA Modernization Act (FDAMA), incorporated the following provision into Section 506 (b) of the Act, which amends the accelerated approval process and permits FDA to approve a therapeutic agent, "… upon a determination that the product has an effect on a clinical end point or on a surrogate end point that is reasonably likely to predict clinical benefit."

This means that when it is not feasible to base the outcome of a clinical trial on an end point of clinically meaningful benefit or on a validated surrogate end point, an unvalidated surrogate end point might be employed under certain circumstances.

Under the accelerated approval process, marketing approval may be granted by the FDA for a pivotal trial in which the primary end point is an unvalidated surrogate marker (a Level 3 outcome measure); however, because this action represents a significant departure from the typical process of marketing approval of a therapeutic agent, it poses significant regulatory issues for the FDA.

Fleming (2005) provides a succinct description of the processes and issues that converge in the granting of accelerated approval by the FDA:

… AA [accelerated approval] [should] be granted only when diseases are life-threatening or induce irreversible morbidity; the new intervention is expected to provide important benefit over existing therapies; the proposed surrogate end point upon which AA will be granted satisfies the criteria for a Level 3 outcome measure; clinical trials are in place at the time of the AA that can reasonably be expected to provide statistically compelling evidence, within a well-defined rapid time frame, about whether the intervention has a favorable benefit-to-risk profile by being safe and by providing clinically meaningful tangible benefit to patients; and the product will be withdrawn from the market promptly if the validation trial does not conclusively provide this required positive evidence.

To reiterate, there are two essential steps involved in the accelerated approval process:

1. Marketing approval of a pivotal trial in which the treatment is shown to have a significant effect on the proposed surrogate end point that is consistent with the expected effect on the target clinical end point
2. A post-marketing study that demonstrates a strong association between the treatment effect on the surrogate end point and the treatment effect on the target clinical end point must be in place at the time of approval of the pivotal trial.

Elements of accelerated approval within the HFC clinical development program

The target clinical end point in the HFC clinical development program is hemostasis in a population of subjects with congenital fibrinogen deficiency, namely, either maintaining hemostasis prophylactically or achieving hemostasis in the event of spontaneous bleeding or bleeding resulting from trauma.

Accelerated approval was sought for the use of HFC in congenital fibrinogen deficiency because of the difficulty of conducting a conventional pivotal clinical trial in this population of subjects. For example, consider a superiority trial intended to demonstrate that HFC is more effective than cryoprecipitate in achieving hemostasis in subjects with congenital fibrinogen deficiency who present with bleeding. Further, suppose that the rate of success in achieving hemostasis is 95% in the group of subjects randomized to receive HFC and 90% in the group of subjects randomized to receive cryoprecipitate and that a level of statistical significance of 5% at 80% power is desired to be achieved in this trial; then, a total of 870 subjects, 435 in each treatment group, would have to be enrolled. The prevalence of congenital fibrinogen deficiency in the general population is estimated to be approximately 1 per million [Mannucci 2004; de Moerloose 2008]; therefore, the estimated prevalence in the United States is approximately 300 patients. Identifying and enrolling into a clinical trial 870 such individuals who are experiencing active bleeding is not feasible.

Non-inferiority trials are often viable alternatives to superiority trials when the effect of a proposed treatment on the target clinical end point is expected to be similar to an existing, approved treatment, and where the new treatment may have a better safety profile or superior convenience. But even a randomized non-inferiority trial of HFC versus cryoprecipitate would require a prohibitively large number of participants: assuming subjects are randomized to a treatment group receiving HFC and a treatment group receiving cryoprecipitate and assuming that the success rate in achieving hemostasis in either group is 95%, and a difference of 5% in the rate of hemostasis is not considered clinically important (ie, non-inferiority margin is set at 5%), then a total of 600 subjects, 300 in each treatment group would need to be enrolled.

Attempting to conduct either a superiority or a non-inferiority trial of hemostasis in prophylaxis for spontaneous bleeding in a population of subjects with congenital fibrinogen deficiency, (comparing HFC and cryoprecipitate) where the annual event rate for spontaneous hemorrhage is low (but where one event, such as a spontaneous intracranial hemorrhage, can be fatal), would require a trial of prohibitive size and duration.

Therefore, because the size and/or duration of a traditional clinical trial in a population of subjects with congenital fibrinogen deficiency was not feasible and because a number of biological markers with the potential to be surrogate end points in this indication were known to exist as a result of CSL Behring's experience with Haemocomplettan® P (the counterpart to HFC that is marketed outside of the United States in 12 countries), CSL Behring elected to pursue accelerated approval as part of the clinical development strategy for HFC. The critical first step in this process was the selection of a biological marker that would serve as a suitable candidate for a surrogate end point for the target clinical end point of hemostasis.

The biological marker selected for use in the HFC development program is MCF as measured by the thromboelastometry device ROTEM®. As outlined above, the pivotal trial in the accelerated approval process must demonstrate that the treatment with HFC has a significant effect on the proposed surrogate end point consistent with the expected effect on the target clinical end point. In other words, the pivotal trial must demonstrate that fibrinogen replacement therapy via HFC administration produces an effect on MCF (the surrogate end point) that has a plausible biological connection to hemostasis. The argument for such a connection in this case is straightforward: subjects with congenital fibrinogen deficiency lack sufficient amounts of fibrinogen in their blood, or have dysfunctional fibrinogen, which prohibits the formation of viable and stable clots in the event of hemorrhage.

In the pivotal clinical trial (Study 2001), it was shown that HFC raises the level of functioning fibrinogen in study subjects' blood to approximately one-half of the fibrinogen levels found in healthy individuals—people without congenital fibrinogen deficiency. The correlation of fibrinogen activity levels with fibrinogen antigen levels measured in the pivotal trial demonstrates that the replacement fibrinogen supplied to subjects via the infusion of reconstituted HFC is functioning fibrinogen. That the level of fibrinogen is approximately half of that seen in normal people is purposeful: the dose was determined to achieve this effect because it is known from experience in fibrinogen replacement therapy in this population that returning fibrinogen levels to what is considered normal for people without congenital fibrinogen deficiency can make fibrinogen-deficient subjects hypercoagulable, putting them in danger of incurring thrombotic events. Returning fibrinogen levels to below normal physiological levels in patients with congenital fibrinogen deficiency has been shown to provide hemostasis with a low risk of thrombotic complications.

The results of Study 2001 show that, in the per protocol population, MCF increased in 1 hour from 0 to values in the range of 6.5 to 16.5 mm, with a median value of 10.0 mm and a mean value of 10.25 mm. These values were determined from ROTEM® analysis of plasma samples. Plasma samples were used as opposed to whole blood to avoid confounding the clotting effect of fibrinogen with that of platelets on MCF values. Although a reference range for MCF values obtained by ROTEM® has been reported for normal whole blood (Lang 2005), a corresponding range remains to be established for plasma. Kalina et al (2008) report values for MCF obtained by ROTEM® from frozen normal plasma in the range of 23.8 to 28.5 mm. Study 2001 subjects received a dose of HFC calculated to raise their fibrinogen activity level to near the lower limit of normal (experience with HFC indicates that fibrinogen- deficient subjects become hypercoagulable if their fibrinogen level is raised to normal); one would therefore expect that

because of the reduced level of fibrinogen, these subjects' MCF values would be lower than normal, and that is indeed what was observed.

As can be seen in Table 6 (section 5.1.4.2) (which includes data from one subject for whom no 1-hour MCF value was available; therefore, change from baseline was 0), a 1-sample *t*-test for paired observations of the mean change from baseline in the 1-hour post-infusion MCF value was highly statistically significant ($p<0.0001$).

It is reasonable to expect that prior to fibrinogen replacement therapy, fibrinogen-deficient subjects would evince difficulty clotting and, after treatment, clotting ability would return to near normal. If MCF is to serve as a surrogate end point for hemostatic efficacy, then one would expect to observe an MCF value equal to 0 (no clotting ability) in a fibrinogen-deficient subject prior to fibrinogen replacement and an MCF value significantly greater than 0 after replacement therapy, indicating the ability of the blood to clot. This is exactly what was observed in Study 2001.

Thus, Study 2001 serves as the pivotal trial, as described in the outline above, of the accelerated approval process: a significant effect on the proposed surrogate end point (MCF) consistent with what would be expected if the surrogate end point responds to the treatment (fibrinogen replacement) as the target clinical end point (hemostasis) should if, in fact, fibrinogen replacement therapy produces hemostasis.

It then becomes the purpose of the post-marketing Study 3001 to establish the second of the two essential steps involved in the accelerated approval process: demonstration of a strong association between the treatment effect on the surrogate end point and the treatment effect on the target clinical end point. In other words, the results of Study 3001 must establish that there is a strong association between the effects of fibrinogen replacement therapy on MCF and the effects of fibrinogen replacement therapy on hemostasis, to the extent that variations in MCF can be established to correspond to observed variations in hemostasis.

On a fundamental level, this correspondence is to be expected because, without fibrinogen, blood does not form a viable and stable clot and, in the absence of fibrinogen, blood or plasma will have an MCF near or equal to 0. If blood does not clot, hemostasis cannot be achieved. Therefore, if MCF is 0, one would not expect to observe hemostasis.

Of greater concern is the other end of the spectrum: if fibrinogen replacement therapy leads to hemostasis without the occurrence of thromboembolic events, is there a connection between this outcome and MCF? Study 3001 will also address this question, but there is already evidence accumulating in the literature from the use of ROTEM® in various settings that the association of MCF with hemostasis in fibrinogen replacement therapy can be achieved. The Health Technology Assessment [Craig 2007], prepared for the National Health System of Scotland, of the clinical and cost effectiveness of using thromboelastography and thromboelastometry analyzers compared with standard laboratory tests and clinical discretion, concluded with recommendations that thromboelastography/thromboelastometry be used in surgery or trauma settings to ascertain if bleeding is induced by the surgery or injury or by abnormal hemostasis; if

the latter, the recommendation is to use thromboelastography/thromboelastometry to identify the nature of the abnormality. Of particular interest is the report of McCrath et al [2005] on the use of MCF in predicting postoperative thrombotic complications. If MCF is a proper surrogate for hemostasis, then MCF should provide some indication that normal fibrinolysis occurs following clot formation; otherwise subjects are in a pro-thrombotic state. McCrath et al indicate that above-normal MCF values are indicative of the potential for increased occurrences of thrombotic events.

The accumulating evidence in the literature that MCF may be a viable surrogate for hemostasis supports the contention of CSL Behring that Study 3001 is an appropriate study for the post-marketing arm of the accelerated approval process.

Appendix III. Post-marketing surveillance cases of special interest

Post-marketing surveillance case summaries of special interest are described below.

Post-marketing thromboembolic events

Congenital fibrinogen deficiencies

- Case TE2: a 44-year-old (y.o.) male with congenital afibrinogenemia (CD afib) who had been on prophylactic HFC since age of 23. At age 44 years, he developed an arterial occlusion of the left anterior tibial artery. No evidence of acquired hypercoagulability was found. Local lysis with urokinase and percutaneous transluminal angioplasty were successful. Prophylactic treatment with HFC was continued to avoid life-threatening bleeding, and the patient was then started on low-molecular-weight heparin (LMWH). This treatment did not prevent recurrence of thrombosis. The patient was then started on lepirudin and unfractionated heparin, but again thrombosis recurred. He was switched back to LMWH and lepirudin six times, but thrombosis recurred every time. After the sixth thrombotic episode, no further thrombotic events occurred.

  Sponsor Comment: The reason for thrombus formation remains unclear. A possible contributing cause of the recurrences may have been antibody interference with heparin. However, a causal relation to HFC could not be excluded, although it is not likely to have been the sole reason for thrombus formation since further treatment was tolerated without complications.

- Case TE3: a 23-y.o. male with CD afib and multiple hemorrhagic events who received one 1-g dose of HFC and three 1.5-g doses of Clottagen® (fibrinogen concentrate). During this treatment, the patient experienced multiple arterial thromboses. No further information was provided despite several inquiries.

  Sponsor Comment: A concise medical assessment was not possible due to insufficient data. However, Clottagen® (another fibrinogen concentrate product) was administered at higher doses and more frequently, which could provide an alternative causal explanation.

- Case TE4: a 41-y.o. male who had been treated with HFC for CD afib for 2 years. He experienced visual deterioration, and central vein thrombosis of the left eye was diagnosed. No other thromboembolic risk factors were reported.

- Case TE5: a 39-y.o. male with CD afib who had been treated with HFC for more than 15 years. He had a history of cerebral bleeding in 1998. Since then, he had received HFC prophylaxis (6 g every 2 weeks). Ten days after the last dose of HFC, the patient developed paresis of the left hand caused by cortical and subcortical infarctions in the distribution of the middle cerebral artery. In addition, the CT scan showed a small thrombotic seam in the area of the left aortic arch directly lateral of supra-aortic vessels, as well as a thrombus amounting to the bifurcation of aorta pulmonalis. Prophylaxis with HFC was continued in reduced

dosage and antithrombotic therapy was initiated. The treating physicians considered the risk of bleeding without replacement therapy to be greater than the risk of thrombosis associated with replacement therapy.

Sponsor Comment: The prophylactic dose of 6 g every 2 weeks may have been excessive in this patient. Fibrinogen levels were not provided.

- Case TE6: a 32-y.o. female with CD afib who had developed massive hemorrhage after iatrogenic arterial injury. Fibrinogen was replaced with doses of HFC (up to 8 g) and the hemorrhage stopped. The patient developed massive proximal DVT of the left leg, but was successfully treated with fibrinolysis.

- Case TE7: an 18-y.o. female with CD afib, treated with HFC for many years. The patient had a port-a-cath removed from her right forearm and an infusaport implanted into her right chest for venous access. HFC dosing was adjusted to keep her fibrinogen levels at 100 mg/dL in the first postoperative week and at 50 mg/dL in the second postoperative week. Fifteen days after the operation, she was admitted to hospital with a right jugular and SC blood clot and superior vena caval syndrome. Two days later, it was noticed that she had a right lower lung pulmonary embolism. The patient had the infusaport removed and a partial embolectomy was performed. Subsequently she had SC and upper superior vena cava angioplasties with continuation of catheter-directed thrombolysis. Although the patient recovered, she still has residual clots in SC and internal jugular veins. She is now doing well. She remains on Lovenox® (enoxaparin sodium) therapy with frequent infusions of HFC.

  Sponsor Comment: The implantation of the infusaport may provide a contributory explanation for clot formation.

- Case TE8 (from the scientific literature [Langer 2007]): a 69-y.o. male with hypofibrinogenemia was newly diagnosed with acute monocytic leukemia. He developed spontaneous hematoma and hemorrhage from venous puncture sites. To prevent fatal hemorrhage, he received an i.v. bolus of aprotinin, followed by continuous infusion of aprotinin and HFC. Within 48 hours of treatment, he developed microvascular thrombosis and intravascular hemolysis. He recovered following hemodialysis and treatment with cytarabine and heparin.

  Sponsor Comment: The use of concomitant aprotinin treatment may have contributed to this event; aprotinin has been removed from the market because of safety concerns.

- Case TE9 (from the scientific literature [Pati 2008]): a 32-y.o. female with CD afib was admitted to the emergency department with increasing frontal headache and flu-like symptoms over 4 days, culminating in sudden collapse. CT scan revealed large extra- and subdural hematomas. She received 3 g HFC and the hematomas were evacuated. A second craniotomy was performed 12 hours later. After 24 hours, the patient was successfully awakened and extubated. Over the next several weeks she received 2-g infusions of HFC on alternate days. During the third week, she developed dyspnea and pleuritic chest pain. The CT showed bilateral pulmonary emboli. A caval filter was inserted. No further fibrinogen infusions were given.

Acquired fibrinogen deficiencies

- Case TE1: a 15-day-old female with congenital heart defect who had undergone heart surgery including extracorporeal membrane oxygenation (ECMO). She required replacement of partially occluded pulmonalis graft 7 days post-surgery. ECMO had to be restarted after failure to wean from the bypass. In addition to protamine sulfate, the patient received PRBCs, plasma, platelets, activated PCC, ATIII, and HFC. Despite coagulation factor replacement therapy and surgical interventions, pulmonary bleeding continued. Recombinant activated factor VII was administered until sufficient hemostasis was obtained. However, life-threatening bleeding suddenly recurred and the patient died. Autopsy revealed thrombosis of the SC arteries and truncus brachiocephalicus.

  Sponsor Comment: Although a causal relation to HFC cannot be excluded, the administration of various coagulation factors, especially activated factor VII and activated PCC, as well as the mechanical irritation caused by insertion of ECMO catheters, may have been contributed to thrombosis.

Post-marketing cases of death

- Case PVD1: an 81-y.o. male with a history of coronary artery disease underwent cardiac surgery with extracorporeal circulation. Intraoperatively, he received aprotinin for prevention of bleeding, protamine for reversal of heparin effect, and HFC. After an uncomplicated course, the extracorporal circulation was terminated and the heart was decannulated. While suturing the insertion sites of the cannula, the aorta ascendens partially split. A clamp was positioned. After removal of the clamp the patient suddenly developed hypotension, erythema, skin edema, and arrhythmia. He was treated with Fenistil® (dimethpyrindene), ranitidine, prednisolone, dexamethasone, and epinephrine, and was again transferred to extracorporeal circulation. After volume replacement and high-dose therapy with catecholamines, extracorporal circulation was again terminated without problems. Although the following course appeared uncomplicated, the patient died of refractory cardiac failure 2 days later.

  Sponsor Comment: The shock may have been multifactorial, with an allergic reaction aggravated by cardiac failure (due to volume deficit, deficit of oxygen carriers, and a previously damaged myocardium). The cause of death was cardiac failure 2 days after HFC administration; this was not likely related to HFC.

- Case PVD2: an 18-y.o. female with CD afib was admitted to hospital with a cerebral bleed (date not provided). She was treated with 1g HFC BID starting on 11/26/03. On 5/3/03, the patient developed urticarial rash and fever. On 5/7/03, decreased blood pressure, dizziness, and nausea were observed 1–2 hours post-transfusion. However, the rash was improving. On 5/8/03, patient was sleepy, dizzy, and nauseated, but had no rash or fever. Fibrinogen level was 130 mg/dL with an HFC dosage of 1 g/day. On 5/9/03, patient was lethargic, had headache, and vomited. Fibrinogen level was 110 mg/dL, CT displayed cerebral edema. On 5/10/03, patient died as a result of cerebral edema. On 5/7/03, and the following days, the dosage of HFC had been adjusted due to the patient's condition and fibrinogen level.

Sponsor Comment: A causal relation between HFC and the symptoms of an allergic reaction, such as urticarial rash, and fever cannot be excluded. A causal relation between HFC and cerebral edema and its symptoms are unlikely; the cerebral bleed due to afibrinogenemia is an alternative and more probable explanation.

- Case PVD3: see TE1 above.

Post-marketing suspicion of virus transmission cases

Congenital fibrinogen deficiencies

- Case V1: a 40-y.o. female with hypodysfibrinogenemia who received HFC in 1984, 1986, 1987, and 1988. In 1982, she had slightly elevated hepatic transaminases. In 1995, anti-HCV testing was performed for the first time. The result was positive.

  Sponsor Comment: In this case, the time of infection cannot be exactly defined. Before the 1990s, no testing system for anti-HCV existed. Hepatitis C (non-A, non-B hepatitis at that time) had to be diagnosed clinically. The increase in transaminases in 1982 could be an indication of already-existing hepatitis C infection. The patient had received non–virus inactivated products prior to receiving HFC. These products provide an alternative and more probable explanation for infection with hepatitis C. Therefore, a causal relation with HFC is unlikely.

- Case V13: Published as a poster "Afibrinogenemia: Prophylactic Treatment With Fibrinogen Concentrate HFC" for the German Society for Thrombosis and Hemostasis meeting in 2003. The poster reported efficacy and safety of HFC following the first 2 years of treatment in eight patients (from 2001 to 2002). One of the patients displayed an infection with hepatitis C. The author stated that there is absolutely no suspicion that the patient was infected by HFC.

  Sponsor comment: The patient received plasma simultaneously; therefore, the source of the infection is unclear.

Acquired fibrinogen deficiencies

- Case V2: a 61-y.o. male who underwent cardiac surgery on 8/12/94. During surgery he received HFC, three PRBCs, plasma, ATIII, and human albumin. In 9/94, he developed icterus, asthenia, and an increase in liver enzymes. In 6/95, hepatitis C was serologically confirmed for the first time. No further data could be obtained.

  Sponsor comment: The administration of plasma provides an alternative explanation for the source of infection. The donors of PRBCs all tested negative for anti-HCV. No information could be obtained about the plasma.

- Case V3: a female patient (age unknown) who received HFC for a gynecologic intervention in 3/88. Immediately after discharge she tested positive for hepatitis C.

  Sponsor comment: No clinical symptoms or details of HCV serology testing are reported. Therefore, the time of infection remains unclear. A preexisting infection has to be taken into consideration since the patient could have been infected prior to

receiving HFC. In up to 40% of all hepatitis C cases, the source of infection remains unclear.

- Case V4: a 68-y.o.male received HFC for hemorrhagic shock in 1991. In addition to HFC, he received 14 units of PRBCs and 5 units of plasma at that time. In 1996, the following hepatitis B serology was obtained: HBsAg positive, anti-HBc positive, Hepatitis B virus envelope antigen (HBeAg) positive, anti-HBe negative, anti-HBc IgM negative.

  Sponsor comment: Since no previous hepatitis serology exists, the time of infection cannot be exactly defined. The serology obtained in 1996 is not consistent with chronic hepatitis of the post-infection phase. An infection in 1991 is very unlikely.

- Case V5: a male patient (age unknown) treated in 1994 with HFC, PRBCs, and platelets as a result of chemotherapy. Hepatitis C infection was diagnosed. Before chemotherapy, the patient was hepatitis C negative. Despite several inquiries no further information was obtained.

  Sponsor comment: A concise medical assessment is not possible. The patient received PRBCs and platelets; these products provide alternative explanations for HCV infection.

- Case V6: a 40-y.o. male suffering from hepatitis C (date of this diagnosis unknown). He was treated with HFC in 3/96 during heart surgery (3 batches of HFC were possibly administered).

  Sponsor comment: On 2/21/97, all three lots of HFC that might have been administered to the patient were tested by PCR for HCV RNA and all lots were found non-reactive (negative). On 8/21/98, the three lots of HFC were re-tested for HCV RNA (NAT) at the National Reference Center for Hepatitis C in Germany. The negative result of the PCR testing on 2/21/97 was confirmed by the Reference Center. As pasteurization inactivates infectivity but not PCR signal, the non-reactivity for HCV RNA by PCR (NAT) in final containers strongly supports the conclusion that there is no causal relationship between HCV infection and HFC treatment (even a NAT signal in the final container would represent inactivated HCV).

- Case V7: a 22-y.o. male with ALL. He received a total of 26 units of PRBCs, 29 units of platelets, Endobuline® (immunoglobulin human), HFC, ATIII, and human albumin N from 6/96 to 8/97. On 7/4/97, hepatitis B was diagnosed.

  Sponsor comment: The administration of PRBCs or platelets is considered a more possible source for the infection, especially because a screening with a sensitive NAT assay was not performed for these non–virus-inactivated products.

- Case V8: a 62-y.o. female who underwent hip surgery in 2/96. Because of massive intraoperative bleeding, she received PRBCs, PCC, and HFC. In 11/97 she tested positive for HCV.

  Sponsor comment: PCR testing of the administered HFC batch was negative. The patient received other blood/plasma-derived products; these products provide alternative explanations for HCV infection.

- Case V9: a 10-y.o. male patient with ALL who underwent chemotherapy from 3/9/94 to 9/24/94. Testing for hepatitis A, B, and C and HIV were negative. During the same time he also received PRBCs, and platelets. He received HFC between 3/94 and 4/94. In 3/95 and 5/96, he was anti-HCV negative. Two years after HFC treatment (in 6/96), the patient was HCV positive (type of test not yet known). Previous tests were anti-HCV negative (ELISA). In 12/98 a liver biopsy was performed; it showed chronic hepatitis C.

  Sponsor comment: Hepatitis C was diagnosed in 6/96. As the incubation period of hepatitis C is on average approximately 3 weeks (NAT reactivity) to 12 weeks (seroconversion), and the patient was tested anti-HCV negative in 3/95 and 5/96, a treatment with HFC one year earlier could not be the cause of the HCV infection diagnosed in 6/96. Therefore, we exclude a causal relation with HFC.

- Case V10: a female nurse (age unknown) treated with HFC and a non–virus-inactivated product (plasma) during surgery in 1986. Infection with hepatitis C was reported in 2000.

  Sponsor comment: Despite several inquiries no further information was obtained. A causal relation to HFC is unlikely because the patient received a non–virus-inactivated product. This provides an alternative and more likely source of infection. In addition, the patient is a nurse and her professional activity creates a higher-than-usual risk of being infected with hepatitis C. Since there is no information on previous virus tests and their results, the time of infection cannot be specified.

- Case V11: a 28-y.o. female received HFC for caesarean section on 12/30/01. Nine days later, she developed hemorrhagic shock after suction curettage and was treated with human albumin, plasma, and PRBCs. Hepatitis B serology was reported to be negative in 12/01. However, on 3/25/02, she was found to be positive for anti-HBs, anti-HBc, and anti-HBe.

  Sponsor comment: This serology is consistent with a hepatitis B infection previous to the HFC treatment, as anti-HBe and, especially, anti-HBs weere detected approximately 3 months after the treatment. As anti-HBs can be detected beginning approximately 32 weeks post-infection, the patient most probably had been infected with hepatitis B prior to HFC treatment.

- Case V12: a 49-y.o. male received HFC and multiple other blood products from 4/01 to 5/01 for an unknown indication. A suspicion of hepatitis C has been reported in this patient.

  Sponsor comment: A causal relation was assessed as unlikely because the reported lots were manufactured from PCR HCV-negative plasma pool for fractionation; the release of the plasma pool for further processing due to non-reactivity for HCV RNA was confirmed by an OMCL (Official Medicine Control Laboratory). Furthermore, no other reports concerning suspicion of hepatitis C were received for the reported lots.

- Case V14: a 44-y.o. male suffering from multiple trauma and DIC. The patient was hospitalized from 11/17/01 to 12/31/01. On 11/17/01, he underwent surgery, during which he received 2 g of HFC. During hospitalization he additionally received PRBCs, plasma, platelet concentrates, ATIII, Biseko® (serum protein solution), and autologous blood. In 2004,

hepatitis C was diagnosed. The reporting physician assessed a causal relation with HFC as unlikely.

Sponsor comment: A causal relation was assessed as unlikely because the reported lots were manufactured from PCR HCV-negative plasma pool for fractionation; the release of the plasma pool for further processing due to non-reactivity for HCV RNA was confirmed by an OMCL. Furthermore, no other reports concerning suspicion of hepatitis C were received for the reported lots.

Post-marketing possible hypersensitivity reactions

Congenital fibrinogen deficiencies

- Case A1 [same case as reported in Study 501, section 8.4.3]: a 7-y.o. female with congenital hypofibrinogenemia who received 55 infusions of HFC for prophylaxis, which were well tolerated. On the 56th infusion, she developed chills, back pain, abdominal rigidity, tachycardia, hypotension (not specified), and cyanosis and was hospitalized. After treatment with antihistamines and glucocorticoids, the subject had a rise in temperature and vomited; thereafter she recovered. Further administrations of HFC were well tolerated.

- Case A2: a 3.5-y.o. male with CD afib who received prophylactic treatment with HFC since birth. In 10/93, he developed chills, fever, pallor, decreased blood pressure (not specified), tachycardia, cold sweats, restlessness, and fatigue. Even after changing the batch of HFC, the boy developed tremor, pallor, tachycardia, sore throat, tiredness, and chills. After treatment with glucocorticoids and infusion of human albumin, he recovered within 1 to 4 hours.

  Sponsor comment: A causal relation with HFC is probable considering the positive re-exposure.

- Case A3: a 30-y.o. female with CD afib who was prophylactically treated with HFC for years. In 1/94, she was not administered the full dose of HFC because she developed chills, started to tremble, and had a feeling of numbness in her left leg, The numbness in her left leg persisted on the next day and she was admitted to hospital. A cerebral hemorrhage was diagnosed. A subsequent infusion of HFC was well tolerated after premedication. However, the next infusion caused a drop in blood pressure, nausea, heat waves, and a tightness of the chest. She was treated with volume replacement, epinephrine, and glucocorticoids.

  Sponsor comment: A causal relation with HFC is probable considering the positive re-exposure.

- Case A4: a 25-y.o. male with CD afib who developed chills after administration of 4 g HFC. He had tolerated previous infusions of HFC but had a history of allergic reactions to other fibrinogen concentrates. The patient recovered. Re-exposure to HFC did not lead to a reaction.

  Sponsor comment: Although a causal relation is possible, individual batch intolerance is an alternative explanation for the symptoms.

- Case A5: a 33-y.o. male with CD afib who developed fever and chills 30 minutes after administration of HFC. Two previous infusions had also been associated with fever and chills; however, the patient had a viral infection at that time.
  Sponsor comment: A causal relation cannot be excluded because of lack of an alternative explanation and the close temporal relation with HFC.

- Case A7: a 27-y.o. female with CD afib who developed burning in the nose and sneezing after receiving HFC. Subsequent infusions led to chills, sweating, tinnitus, headache, and stomach discomfort. The symptoms abated after treatment with antihistamines and glucocorticoids. The patient switched products.
  Sponsor comment: A causal relation is possible considering the positive re-exposure.

- Case A8: a 13-y.o. male with CD afib who was treated with HFC on demand. In 1/94, he received HFC because of an ankle bleed. Toward the end of infusion, he developed chills and an increase in body temperature. The next infusion was also followed by chills and an increase in body temperature.
  Sponsor comment: A causal relation is highly probable considering the positive re-exposure.

- Case A9: a 14-y.o.female with congenital hypofibrinogenemia who developed chills, pruritus, and tachypnea after administration of HFC. During further HFC treatment, she had no adverse reactions except for a mild increase in temperature.
  Sponsor comment: A causal relation cannot be excluded considering the lack of an alternative explanation and the close temporal relation with HFC.

- Case A10: a 29-y.o. male with CD afib who developed chills 15 minutes after infusion of HFC. The symptoms subsided without treatment.
  Sponsor comment: A causal relation cannot be excluded considering the lack of an alternative explanation and the close temporal relation with HFC.

- Case A11: a 16-y.o. male with hypodysfibrinogenemia with shivering and nausea at the end of HFC infusion. He was hospitalized, but the symptoms subsided without treatment.
  Sponsor comment: A causal relation cannot be excluded considering the lack of an alternative explanation and the close temporal relation with HFC.

- Case A12: a 5-y.o. female with CD afib receiving prophylaxis with HFC. Previous treatments with HFC had been well tolerated. She developed sudden vomiting, nausea, pallor, and tachycardia 30 minutes after administration of HFC. She recovered after treatment with antihistamines and glucocorticoids.
  Sponsor comment: A causal relation cannot be excluded considering the lack of an alternative explanation and the close temporal relation with HFC.

- Case A15 [see Case D2]: Possible allergic symptoms were urticarial rash/fever. Cause of death was cerebral edema/bleeding.
  Sponsor comment: A causal relation between HFC and development of urticarial rash/fever is possible.

- Case A16: a patient (age and gender unknown) who was treated with HFC (indication, dose, and date unknown). Patient developed an allergic reaction. No more details were provided.
  Sponsor comment: A causal relation between the allergic reaction and HFC could not be assessed with the data provided. Despite several inquiries, no further information was obtained.

- Case A17: a 29-y.o. female with CD afib who developed swelling of the uvula, itching, burning esophagus, dysphagia, white skin swelling, foot edema, and stabbing heart pain 2 hours after HFC administration. The symptoms subsided after treatment with antihistamines. Prior to subsequent infusions of HFC, the patient was supposed to take antihistamines as premedication but she forgot to do so. The same symptoms recurred following another infusion and subsided after treatment with antihistamines and glucocorticoids. All further infusions were tolerated well with premedication.
  Sponsor comment: Considering the positive re-challenge, the causality with HFC was assessed as probable.

- Case A18: a female (age unknown) with CD afib who received HFC on a monthly basis (dose, treatment dates, and lot number not provided). She developed adverse reactions such as rash, fever, hypertension, tachycardia, and loin pain. The symptoms did not occur with every infusion.
  Sponsor comment: A substantiated medical assessment is not possible with the limited data provided.

- Case A19: a 17-y.o. female with congenital afibrinogenemia who experienced exanthema, nausea, vomiting, dizziness, syncope, thoracic pain, and headache after administration of HFC. She recovered after treatment with antihistamines and glucocorticoids.
  Sponsor comment: A causal relation cannot be excluded because of the lack of an alternative explanation and the close temporal relation with HFC.

Acquired fibrinogen deficiencies

- Case A6: a 56-y.o. male with a dissected aorta (type I) who was treated with HFC after lysis therapy with streptokinase (indication unknown). After infusion of 3 g HFC on 2/21/94, the patient developed tachycardia, a drop in blood pressure, bronchoconstriction, and increased body temperature (up to 101.3 °F). The reporting physician suspected anaphylactic shock. The patient recovered within 30 minutes after having been treated with glucocorticoids, antihistamines, and oxygen.
  Sponsor comment: A substantiated medical assessment is not possible with the limited data provided. Lysis is contraindicated in patients with a dissected aorta. Shock was possibly hemorrhage related. Streptokinase is also a potential etiology for anaphylaxis.

- Case A13: see PVD1 above.

- Case A14: a 72-y.o. (gender unknown) treated with HFC during cardiac surgery because of severe bleeding. Three minutes after start of the infusion, the patient developed severe

shaking. HFC was discontinued and restarted 5 minutes later. Again the patient developed shaking.

Sponsor comment: A causal relation is probable considering the positive re-exposure.

- Case A20: a 30-y.o. male who underwent cardiac surgery for mitral valve prolapse in 3/08. Perioperatively, he received 35,000 units of protamine. After closure of the surgical wound, he received HFC (batch number, dose, and indication not specified) and immediately experienced a drop in blood pressure to below 30 mm Hg. He developed anaphylactic shock, respiratory arrest, and cardiac arrest. Cardiac massage was performed. On 4/22/08, he was transferred to the dermatology department for skin prick testing with HFC batch no. 01468011A. Testing was performed using dilutional series, and he showed pronounced skin reactions, even with dilutions of 1:100. Testing of the same batch was performed in three healthy subjects without any reaction. The treating physician suspects that the skin reaction is not batch related but a reaction against the HFC product. The patient is scheduled to return to the dermatology department for further skin testing of the other drug products that he received concomitantly.

  Sponsor comment: This case is still under evaluation. However, due to the close temporal relation and the positive skin prick test, causality cannot be excluded.

Appendix IV. Non–treatment-related deaths in observational case collections

Observational acquired deficiency case collection, Study 7D-501 (1993–1995)

Table 21. Summary of death cases in acquired fibrinogen deficiency observational study 7D-501 (1993–1995) (no death was assessed as being related to HFC by investigators)

Case No.	Age (yrs)	Reason for AD (Major Symptoms/Underlying Conditions)	Total Dose/Daily Dose of HFC (g/g per day)	Time Between Last HFC Dose and Death (days)	Cause of Death
D1	17	DIC due to severe head trauma (craniofacial, pulmonary, retroperitoneal bleeding due to trauma)	2/2	4	Cerebral death due to head trauma
D2	53	DIC due to multiple trauma (craniocerebral, hemothorax, etc)	1/1	1	Cerebral death due to head trauma
D3	28 wks* gestation	Amniotic infection syndrome, sepsis	0.1/0.05	5	Neonatal respiratory distress syndrome, bronchopulmonary dysplasia, hypoxia, pneumothorax
D4	24 wks* gestation	Immature liver (intraventricular hemorrhage)	0.26/0.05	2	Hypoxia, bradycardia
D5	76	DIC, hemorrhagic shock, and bleeding at puncture sites due to coagulopathy (renal failure, COPD, liver disease, suspicion of chronic passive liver congestion)	2/2	8	Cardiopulmonary decompensation
D6	33	Coagulopathy due to liver cirrhosis/hemorrhagic diathesis (epistaxis, GI bleeding, oral/pharyngeal hematoma)	18/6	10	Central regulation failure due to intracranial (intraventricular) hemorrhage
D7	68	DIC and hemorrhagic shock due to rupture of Glisson's capsule (postoperative bleeding after a cholecystectomy, bile duct revision, and pancreas biopsy)	6/6	39	Cardiovascular arrest caused by sepsis
D8	54	Coagulopathy due to liver cirrhosis, sepsis with hemorrhage requiring 21 U PRBCs (AML)	19 (over 13 days)	15	Hepatorenal failure, AML
D9	64	Thrombolytic tx for AMI	2/2	2	Intracerebral hemorrhage 2° to thrombolytic tx for AMI

Case No.	Age (yrs)	Reason for AD (Major Symptoms/Underlying Conditions)	Total Dose/Daily Dose of HFC (g/g per day)	Time Between Last HFC Dose and Death (days)	Cause of Death
D10	77	DIC, consumptive coagulopathy, postoperative bleeding after hip replacement surgery (hx of chronic cardiac insufficiency)	4/~1	2	Myocardial infarction
D11	43	DIC, acute liver failure (hypovolemic shock/cirrhosis)	16/4	6	Cardiac failure
D12	65	DIC, postoperative bleeding (cardiac failure)	4/~1	0	Cardiac failure
D13	46	Liver disease and asparaginase treatment for ALL	10/NA	30	Fulminant interstitial pneumonia due to immunosuppress-ants
D14	72	Thrombolytic tx for AMI; disturbance of coagulation	2/2	2	Small intestine ischemia 2° to bowel hemorrhage, a complication of thrombolytic therapy
D15	36	Hepatic synthesis disorder due to asparaginase treatment for ALL	15 (over 7 days)	18	Clotting disorder and cerebral hemorrhage
D16	35	Acute hemorrhage of intracranial cavernous malformation	4/4	6	Pulmonary failure with pulmonary mycosis
D17	65	Acute leukemia	8/~2	25	Pulmonary failure
D18	56	Coagulopathy due to cirrhosis and DIC (hemorrhagic antral gastritis)	10/~2	35	Cardiac failure and hepatic coma
D19	43	Coagulopathy due to cirrhosis	3 (over 12-days)	3	Uncontrollable bleeding from esophageal varices and duodenal ulcer
D20	36	Coagulopathy due to cirrhosis	14/7	1	Severe bleeding from esophageal varices

AD = acquired deficiency; ALL = acute lymphoblastic leukemia; AMI = acute myocardial infarction; AML = acute myeloid leukemia; COPD = chronic obstructive pulmonary disease; DIC = disseminated intravascular coagulation; GI = gastrointestinal; hx = history; NA = not available; tx = treatment; wks = weeks; yrs = years.

- Case D1: a 17-y.o. male with a 2- to 3-year history of drug addiction was admitted to the hospital due to DIC, shock, and craniocerebral trauma caused by a jump, with craniofacial, pulmonary, and retroperitoneal bleeding. The patient received a single dose of 2 g HFC one day after hospital admission. Baseline fibrinogen level was 46 mg/dL. Relevant concomitant meds included 1000 IU ATIII, 500 mL plasma, 12,000 IU/day heparin, whole blood (amount unknown), and platelets (amount unknown). Fibrinogen level returned to 262 mg/dL 3 days

prior to death (normal levels are 200–450 mg/dL). The patient died 4 days after the HFC dose due to cerebral death.

  - *Sponsor Comment:* DIC following severe head trauma has been documented to develop within 1 to 4 hours after brain injury, and is associated with a higher frequency of death.

- Case D2: a 53-y.o. male admitted for multiple trauma (multiple bone fractures, craniocerebral trauma, hemothorax, lung injuries caused by rib fractures), DIC, and hemorrhage. The patient received a single dose of 1 g HFC on the day of admission. Baseline fibrinogen level was 44 mg/dL. Fibrinogen level returned to 332 mg/dL on the next day. Relevant concomitant meds included 400 IU PCC, 12,000 IU heparin, and 2000 mL whole blood. The patient died 1 day after the HFC dose due to cerebral death.
  - *Sponsor Comment:* DIC following severe head trauma has been documented to develop within 1 to 4 hours after brain injury, and is associated with a higher frequency of death.

- Case D3: a premature female (28 weeks' gestation) developed amniotic infection syndrome and sepsis. The patient received a total dose of 100 mg HFC (50 mg/day) on two days. Baseline fibrinogen level was 80 mg/dL. Fibrinogen level returned to 300 mg/dL after the first treatment but decreased again to 170 mg/dL prior to the second substitution. Three days prior to death, fibrinogen levels were 260 mg/dL. Relevant concomitant meds included 100 IU ATIII, 200 IU/kg /day heparin, and PRBCs (amount unknown). The patient died 5 days after the last HFC dose due to respiratory distress syndrome, bronchopulmonary dysplasia, hypoxia, and pneumothorax.
  - *Sponsor Comment*: Respiratory distress syndrome with hypoxia is a common cause of death in premature newborns.

- Case D4: a premature female (24 weeks' gestation) was diagnosed with an immature liver on the day of birth and suffered from intraventricular hemorrhage 2 days later. The patient received a total dose of 260 mg HFC over a treatment period of 9 days. Fibrinogen level was 100 mg/dL at baseline and increased to 180 mg/dL after treatment. Relevant concomitant meds included 230 IU ATIII, 200 IU/kg of birth weight/day heparin, and PRBCs (amount unknown). The patient died 2 days after the last HFC dose due to hypoxia and bradycardia.

- Case D5: a 76-y.o. male with a history of renal failure (due to cirrhosis), liver disease, and obstructive chronic bronchitis with emphysema was admitted to the hospital because of suspicion of chronic passive liver congestion. On the day after hospital admission, he suffered from hemorrhagic shock and bleeding at the puncture sites due to coagulopathy. The patient received a single dose of 2 g HFC on this day. Fibrinogen level at baseline was 84 mg/dL and increased to 327 mg/dL after treatment. Subsequently they decreased again to 108 mg/dL 3 days prior to death. Relevant concomitant meds included 800 mL plasma, PRBCs (amount unknown), and 10,000 IU/day heparin. The patient died 8 days after the HFC dose due to cardiopulmonary decompensation.

- Case D6: a 33-y.o. male with a history of cirrhosis (deficiency of α_1-antitrypsin; alcohol abuse), was admitted to the hospital because of hematomas of the floor of the mouth and the pharynx, epistaxis, GI bleeding, and acute hepatic decompensation. The patient received a total dose of 18 g HFC (daily dose of 6 g) over 3 days, starting on the day of hospital admission. Baseline fibrinogen level was 0 mg/dL. Fibrinogen levels reached a maximum of 156 mg/dL and decreased again to 125 mg/dL 6 days prior to death. Relevant concomitant meds included 11,000 IU ATIII, 7000 IU PCC, 1000 mL plasma, 4 units of PRBCs, and 1 unit of platelets. The patient died 10 days after the last HFC dose due to central regulation failure after ventricular bleeding.

- Case D7: a 68-y.o. female with a history of chronic pancreatic fibrosis, cholecystolithiasis, and arterial hypertension was admitted to the hospital because of DIC and hemorrhagic shock due to a rupture of Glisson's capsule and postoperative bleeding after cholecystectomy, bile duct revision, and pancreas biopsy. The patient received a single dose of 6 g HFC on the day of this diagnosis. Baseline fibrinogen level was 91 mg/dL and increased to 454 mg/dL after treatment. Relevant concomitant meds included 500 IU ATIII, 400 IU PCC, 400 mL plasma, 15,000 IU heparin, and 6 units of PRBCs. The patient died 39 days after the HFC dose due to cardiovascular arrest caused by sepsis.

- Case D8: a 54-y.o. male with a history of cirrhosis was admitted to the hospital due to sepsis with hemorrhagic diathesis. He experienced multiple hematomas and oozing hemorrhage at puncture sites during the 6-day period after admission. Baseline fibrinogen level was <20 mg/dL. Fibrinogen level increased to a maximum of 141 mg/dL 16 days prior to death. The patient received a total dose of 19 g HFC (daily dose of 2 g) over 13 days starting on the day of hospital admission. Relevant concomitant meds included 21,000 IU ATIII, 3500 mL plasma, 10,000 units of heparin, 2000 IU factor XIII, 21 units of PRBCs, 51 units of platelets, and 750 mg tranexamic acid. Two days after hospital admission, the patient was diagnosed with acute myeloid leukemia (AML) and received chemotherapy for 9 days starting on the day of diagnosis. The patient died 15 days after the last HFC dose due hepatorenal failure and AML.
    - *Sponsor Comment:* Time interval between HFC treatment and death is too long for there to be a causal relationship.

- Case D9: a 64-y.o.male with a history of hypertension experienced acute myocardial infarction (AMI) and was treated with 1.5 million IU streptokinase. Recurrent infarction 2 days later was managed with 2.4 million IU urokinase. Seven hours later, acute cerebral hemorrhage was diagnosed, and the patient received treatment with a total dose of 2 g HFC (2 doses of 1 g). Baseline fibrinogen level was 30 mg/dL. Fibrinogen level rose to 392 mg/dL on the day of death. Relevant concomitant meds included heparin, metoprolol, nitroglycerin, plasma, PCC, furosemide, and morphine. The patient died 2 days after the HFC dose due intracerebral hemorrhage.
    - *Sponsor Comment:* Intraventricular hemorrhage was caused by thrombolytic therapy.

- Case D10: a 77-y.o. male with a history of arterial hypertension, chronic cardiac insufficiency, and prostate adenoma developed postoperative bleeding (after total hip replacement) and DIC. The patient received a total dose of 4 g HFC over 2 days, starting on the day of diagnosis of DIC. Baseline fibrinogen level was 137 mg/dL. Fibrinogen level increased to 206 mg/dL on the day prior to death. Relevant concomitant meds included 3000 IU ATIII, 2000 mL plasma, 5000 IU/day heparin, PRBCs, and fresh blood (doses not reported). The patient died 2 days after the last HFC dose due myocardial infarction.
    - *Sponsor comment:* Fibrinogen levels were within normal range prior to death. There is no indication that myocardial infarction is connected to a hypercoagulable state. Most likely it is a complication of pre-existing disease.

- Case D11: a 43-y.o.male with a history of cirrhosis and chronic bronchitis developed acute hepatic decompensation and DIC and subsequent hypovolemic shock. The patient received a total dose of 16 g HFC (daily dose 4 g) over 5 days, starting on the day of diagnosis. Baseline fibrinogen level was 102 mg/dL. Fibrinogen level increased to 186 mg/dL on the day prior to death. Relevant concomitant meds included 10,000 IU ATIII, 1700 IU PCC, 6500 mL plasma, 7500 IU/day heparin, and factor XIII, PRBCs, platelets, and fresh blood (doses not reported). The patient died 6 days after the last HFC dose due cardiac failure.
    - *Sponsor Comment:* Cardiac failure is a complication of hypovolemic shock.

- Case D12: a 65-y.o. female with a history of arterial hypertension and cardiac insufficiency developed postoperative bleeding and DIC. The patient received a total dose of 4 g HFC (daily dose approximately 1 g) over 3 days starting on the day of diagnosis. Baseline fibrinogen level was 135 mg/dL. Fibrinogen level increased to 268 mg/dL on the day of death. Relevant concomitant meds included 2500 IU ATIII, 1000 IU PCC, 2500 mL plasma, 5000 IU/day heparin, 6 units of PRBCs, 24 units of platelets, factor XIII, and fresh blood (doses not reported). The patient died on the day of the last HFC dose due to cardiac failure.
    - *Sponsor Comment:* Cardiac failure is due to the underlying disease.

- Case D13: a 46-y.o. female with a disorder of fibrinogen synthesis due to liver disease and treatment of ALL with asparaginase. The patient received a total dose of 10 g HFC over 14 days, starting approximately 1 month after diagnosis of ALL and approximately 20 days after diagnosis of liver disease. Baseline fibrinogen level was 70 mg/dL. Fibrinogen levels did not increase; on the day prior to death the level was 76 mg/dL. Relevant concomitant meds included 7500 IU ATIII, 1500 mL plasma, and 2 units of PRBCs. The patient died 30 days after the last HFC dose due to fulminant interstitial pneumonia resulting from ALL-related immunosuppression.
    - *Sponsor Comment:* Time interval between administration of HFC and death was too long for there to be a causal relationship.

- Case D14: a 72-y.o. male with a history of bronchitis and cardiac failure. The patient received lysis therapy for myocardial infarction. In addition, enteritis was diagnosed on the same day. Complications due to coagulation disorder included intestinal hemorrhage 1 day after the aforementioned diagnoses, for which the patient received a single dose of 2 g HFC. Baseline fibrinogen level was 45 mg/dL. Fibrinogen level increased to 344 mg/dL on the day

of death. Relevant concomitant meds included 4 units of PRBCs. The patient died 2 days after the HFC dose due to small intestine ischemia as a result of bowel hemorrhage.

- *Sponsor Comment:* Bowel hemorrhage was caused by underlying disease (coagulation disorder resistant to treatment).

- Case D15: a 36-y.o. female with a history of arterial hypertension developed a hepatic synthesis disorder due to asparaginase treatment for ALL, resulting in fibrinogen deficiency. The patient received a total dose of 15 g HFC (daily dose 3 g) over 7 days, starting 1 day after diagnosis of synthesis disorder and fibrinogen deficiency. Fibrinogen level at baseline was 37 mg/dL. Despite 4 treatments with HFC, fibrinogen levels ranged between 62 mg/dL and 38 mg/dL on the day of diagnosis of pulmonary embolism. The highest level recorded was 196 mg/dL, 21 days before her death. Relevant concomitant meds included 8000 IU ATIII, 1200 mL plasma, and 15,000 IU/day heparin. As a complication of the clotting disorder, the patient experienced pulmonary embolism on the fifth day of HFC treatment. She died due to clotting disorder and cerebral hemorrhage 18 days after the last HFC dose.
    - *Sponsor Comment:* Time interval between administration of HFC and death was too long for there to be a causal relationship.

- Case D16: a 35-y.o. female with acute hemorrhage of intracranial cavernous malformation who developed bronchopneumonia 15 days later. The diagnosed fibrinogen deficiency was treated with a total dose of 4 g HFC 2 days after onset of bronchopneumonia. Baseline fibrinogen level was 150 mg/dL. Fibrinogen level increased to 370 mg/dL on the day prior to death. Relevant concomitant meds included 6000 IU ATIII, 600 mL plasma, 1 unit of PRBCs, 500 IU PCC, and 15,000 IU heparin. The patient died 6 days after the last HFC dose due to pulmonary failure with pulmonary mycosis.
    - *Sponsor Comment:* Pulmonary failure was associated with bronchopneumonia.

- Case D17: a 65-y.o. female with acute leukemia, treated with asparaginase and a total dose of 8 g HFC (daily dose of approximately 2 g) over the last 5 days of asparaginase treatment. Baseline fibrinogen level was 52 mg/dL. Fibrinogen level increased to 156 mg/dL 23 days prior to death. Relevant concomitant meds included 1800 IU ATIII, 7200 IU/day heparin, and platelets (dose not reported). The patient died due to pulmonary failure 3 1/2 weeks after the last HFC dose.
    - *Sponsor Comment:* Time interval between administration of HFC and death was too long for there to be a causal relationship.

- Case D18: a 56-y.o. male with cirrhosis who, due to impaired liver synthesis and DIC, received a total dose of 10 g HFC (daily dose approximately 2 g) over 6 days, starting approximately 1 month after cirrhosis diagnosis. Baseline fibrinogen level was 134 mg/dL. Fibrinogen level increased to 235 mg/dL 5 weeks prior to death. Relevant concomitant meds included 24,000 IU ATIII, 19,800 IU PCC, 27,000 mL plasma, 12,000 IU/day heparin, and 13 units of PRBCs. On the third day of HFC administration, the patient developed hemorrhagic antral gastritis. He died 5 weeks after the last HFC dose due to hepatic coma and cardiac failure.

- *Sponsor Comment:* Time interval between administration of HFC and death was too long for there to be a causal relationship.

- Case D19: a 43-y.o. female with a history of cirrhosis who developed acute GI hemorrhage due to esophageal varices and duodenal ulcer. Because of impaired fibrinogen synthesis, the patient received a total dose of 3 g HFC over 12 days. Baseline fibrinogen level was 67 mg/dL. Fibrinogen level increased to 176 mg/dL 8 days prior to death. Relevant concomitant medication included 9500 IU ATIII, 13,500 IU PCC, 7200 mL plasma, 39 units PRBCs, and 18 units platelet concentrate. The patient died 3 days after the last HFC dose due to uncontrollable bleeding caused by esophageal varices and duodenal ulcer.
    - *Sponsor Comment:* Bleeding was caused by esophageal varices resistant to treatment.

- Case D20: a 36-y.o. male, with a history of alcoholic cirrhosis, presented with hemorrhagic shock from acute bleeding of esophageal varices. Due to the underlying clotting disorder, the patient received a total dose of 14 g HFC over 2 days (daily doses of 8 and 6 g). Baseline fibrinogen level was <50 mg/dL. Relevant concomitant medication included 5000 IU ATIII, 10,500 IU PCC, 800 mL plasma, 14 units PRBCs, and 2 units platelets. The patient died due to therapy-resistant bleeding from the esophageal varices 1 day after the last HFC dose.
    - *Sponsor Comment:* Bleeding was caused by esophageal varices resistant to treatment.

Congenital and acquired deficiency case collection (1984–1986)

An observational case collection was conducted from 1984 to 1986 that included at least 37 congenital and acquired fibrinogen deficiency subjects. This case collection was conducted by a German marketing organization. The safety information is not complete; no summary tables or study report is available. There were a total of 7 AEs; no event was reported to be related to HFC. The cases that resulted in death are summarized below; all occurred in acquired fibrinogen deficiency.

Table 22. Summary of death cases in congenital and acquired deficiency case collection (1984–1986) (no death was assessed as being related to HFC by treating physicians)

Case No.	Age (yrs)	Reason for AD/Underlying Diseases	Total Dose/Daily Dose of HFC (g/g per day)	Time Between Last Dose and Event	Cause of Death/Description of AE
CC1	60	DIC and hyperfibrinolysis due to malaria	2/2	3 hrs	Cardiac arrest as complication of malaria or alternatively, tx of malaria with quinidine
CC2	75	DIC/sepsis	2/2	3 days	Respiratory insufficiency due to sepsis
CC3	70	Carcinoma	4/4	--	Unknown/drug induced thrombocytopenia

Case No.	Age (yrs)	Reason for AD/Underlying Diseases	Total Dose/Daily Dose of HFC (g/g per day)	. Time Between Last Dose and Event	Cause of Death/Description of AE
CC4	68	Trauma with multiple fractures, head trauma, and bowel perforation	2/2	"night after treatment"	Multiple trauma/head trauma

AD = acquired deficiency; AE = adverse event; DIC = disseminated intravascular coagulation; HFC = human fibrinogen concentrate; tx = treatment; yrs = years.