Blood Products Advisory Committee

Fibrinogen Concentrate (Human), for the Treatment of Congenital Fibrinogen Deficiency

BLA 125317

CSL Behring
January 9, 2009
Introduction

Paul Hartmann, RPh
Sr. Director and Head, US Regulatory Affairs
Research and Development

CSL Behring
Agenda

Medical Need
■ Amy Shapiro, MD: Indiana Hemophilia and Thrombosis Center, Indianapolis, Indiana

Clinical Program
■ Christian Peters, MD, PhD: Sr. Director and Head, US Research and Development, CSL Behring

Clinical Perspective
■ Marilyn Manco-Johnson, MD: Professor of Pediatrics, Director, Hemophilia and Thrombosis Center, University of Colorado Denver
Experts Available for Questions

- Lawrence Goodnough, MD
  Professor of Pathology and Medicine, Director, Transfusion Service, Stanford University;
  Associate Medical Director, Stanford Blood Center

- Patricia Robinson, MD
  Consultant, Drug Safety and Benefit Risk Management
Proposed indication: treatment of congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia; not indicated for dysfibrinogenemia

A purified, heat-treated fibrinogen concentrate from US sourced and virus-screened plasma

Validated virus inactivation / elimination steps

- Al(OH)_3 adsorption
- Heat treatment (60°C for 20 hours)
- Two glycine precipitation steps
## FC Composition

<table>
<thead>
<tr>
<th>Components</th>
<th>Amount per 1-gram Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human fibrinogen</td>
<td>900–1300 mg$^a$</td>
</tr>
<tr>
<td>Human albumin (protein stabilizer)</td>
<td>400–700 mg</td>
</tr>
<tr>
<td>L-arginine hydrochloride (amino acid stabilizer)</td>
<td>375–600 mg</td>
</tr>
<tr>
<td>Sodium chloride (electrolyte)</td>
<td>200–350 mg</td>
</tr>
<tr>
<td>Sodium citrate (electrolyte)</td>
<td>50–100 mg</td>
</tr>
</tbody>
</table>

$^a$ Actual amount listed on vial.
History of FC Outside the United States

- FC marketed by Behringwerke in Germany and Austria since 1986 with the trade name “Haemocomplettan® P”
- Now marketed in 12 countries
- Since approval, ~1 million grams distributed
- Proposed US trade name is “RiaSTAP™”
Regulatory History of FC in the United States

■ June 2002: pre-IND meeting
  – CBER challenged PK end point
  – CBER proposed a cross-over study design
  – CBER stated the need for a retrospective physicians’ survey

■ June 2005: rare disease workshop
  – Identified challenges to product development
  – Identified new opportunities and ideas

CBER=Center for Biologics Evaluation and Research; IND=investigational new drug; PK=pharmacokinetic.
Regulatory History of FC in the United States (Cont’d)

- September 2005: sponsor / FDA rare disease meeting
  - Surrogate end point study
  - Confirmatory study
  - Existing supportive non-IND data

- July 2006: 2nd pre-IND meeting
  - Accelerated approval (Subpart E, 21 CFR 601.41)
  - Pivotal study with maximum clot firmness (MCF) by rotational thromboelastometry (ROTEM®) and PK parameters (Study 2001)
  - Confirmatory post-marketing study to demonstrate hemostatic efficacy (Study 3001)
Regulatory History of FC in the United States (Cont’d)

- November 2006: IND submission
  - PK / MCF study
  - Post-marketing study to verify results

- March 2008: orphan designation
  - “Treatment of fibrinogen-deficient patients”

- July 2008: BLA submission

- January 2009: expected BLA approval

BLA=Biologics License Application.
FC US Clinical Program

- Answers the call put forth by both regulators and those who advocate on behalf of patients with unmet medical needs
- Provides an example of transforming wishes, expressed during 2005 workshop, into reality
- Offers an important and much needed addition to current treatment options
- Will potentially change the lives of US patients with congenital fibrinogen deficiency
Need for Improved Fibrinogen Deficiency Treatment Options

Amy Shapiro, MD
Medical Director, Indiana Hemophilia and Thrombosis Center
Indianapolis, Indiana
Co-Chair, Rare Bleeding Disorder Subcommittee of MASAC
Adjunct Professor of Pediatrics,
Michigan State University
Structure of a Normal Blood Clot

Incidence of Congenital Fibrinogen Deficiency in the United States

- Estimated ~1 case per million people\(^a\) (~150–300 patients)
  - Data collected in HTCs: 94 patients\(^b\)
  - Data collected in UDC: 28 patients\(^b\)

\(^a\) Rare bleeding disorder database. Available at: http://www.rbdd.org/.
\(^b\) Updated November 2008.
HTC=Hemophilia Treatment Center; UDC=Universal Data Collection.
## Relative Frequency of Bleeding Symptoms in 55 Patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Hemophilia A</th>
<th>Afibrinogenemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical cord bleeding</td>
<td>0</td>
<td>44 / 55 (80%)</td>
</tr>
<tr>
<td>Muscle hematoma</td>
<td>93 / 100 (93%)</td>
<td>40 / 55 (73%)</td>
</tr>
<tr>
<td>Oral cavity bleeding</td>
<td>55 / 100 (55%)</td>
<td>40 / 55 (73%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>50 / 100 (50%)</td>
<td>40 / 55 (73%)</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>N/A</td>
<td>14 / 20 (70%)</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>86 / 100 (86%)</td>
<td>30 / 55 (55%)</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>36 / 100 (36%)</td>
<td>23 / 55 (42%)</td>
</tr>
<tr>
<td>Central nervous system bleeding</td>
<td>4 / 100 (4%)</td>
<td>3 / 55 (5%)</td>
</tr>
<tr>
<td>Thrombotic symptoms</td>
<td>0</td>
<td>2 / 55 (4%)</td>
</tr>
<tr>
<td>Urinary tract bleeding</td>
<td>12 / 100 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>10 / 100 (10%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Ordered by descending frequency in hemophilia A. N/A=not applicable.*

## Current Treatment Options for Rare Bleeding Disorders in the United States

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FVIII Deficiency (Hemophilia A)</th>
<th>FIX Deficiency (Hemophilia B)</th>
<th>Fibrinogen Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single protein</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Virus inactivation</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Precise dosing</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Fast preparation</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Small volume</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>1st virus inactivated single protein</td>
<td>1983</td>
<td>1992</td>
<td>?</td>
</tr>
<tr>
<td>1st recombinant</td>
<td>1992</td>
<td>1997</td>
<td>?</td>
</tr>
<tr>
<td>No. of products on US market</td>
<td>7 FVIII concentrates</td>
<td>3 FIX concentrates</td>
<td>0 FI concentrates; cryoprecipitate, plasma</td>
</tr>
</tbody>
</table>
Limitations of Current Treatment Options

Cryoprecipitate and Plasma

- Virus transmission risk
- Exposure to unnecessary proteins
  - Immune reactions (allergic / anaphylactic reaction, hemolysis, or transfusion-related lung injury)
  - Cryoprecipitate contains other unneeded factors, which theoretically increase risk of thromboses
- Transfusion-associated circulatory overload
  - Larger volumes of plasma required to achieve fibrinogen level
- Imprecise dosing, since cryoprecipitate and plasma fibrinogen content not measured
- Product preparation time
- Burden for patient care
Manufacturers should take necessary steps to ensure the continued availability of plasma-derived clotting factor concentrates for individuals with rare bleeding disorders

Such concentrates
- Are safer than the alternatives of plasma and cryoprecipitate, which are not virus attenuated
- Provide the ability to raise clotting factor levels to 100% without the risk of volume overload, which is another drawback of plasma
- Allow for prophylactic treatment, if indicated by severity of the disease and frequency of bleeding episodes

MASAC=Medical and Scientific Advisory Council of the National Hemophilia Foundation.
Clinical Program

Christian Peters, MD, PhD
Sr. Director and Head,
US Research and Development
CSL Behring
Manufacturers should work towards development of pathogen-safe clotting factors for rare bleeding disorders.

Such clotting factors would allow for:
- Individualized treatment of each specific clotting-factor deficiency
- Increased safety from possible transmission of virus and other infectious agents
FC Clinical Studies for US Registration

- **US development program**
  (Accelerated approval process agreed upon by CBER)
  - Retrospective (physician survey 1221; 2002–03)
  - Pivotal PK, efficacy, and safety (Study 2001; 2007–08)
  - Post-marketing study (Study 3001; ongoing)

- **Supportive**
  - Prospective PK (Study 101; 1993)
  - Prospective virus safety (Study 402; 1985–87)
  - Retrospective efficacy (Study 501; 1985–92)
Physician Survey 1221: Retrospective Survey of Physicians

- 34 physicians
- 100 treated patients with congenital fibrinogen deficiency
- 10 countries (8 US centers with 13 patients)
- Gather fibrinogen levels and duration of treatment for minor / major bleeding events
  - Provides historical cryoprecipitate control group for post-marketing study 3001
Physician Survey 1221: Bleeding Frequencies
Episodes (N=517)

Spontaneous 62.3%
Surgery 15.3%
Trauma 19.3%
Unspecified 3.1%
Physician Survey 1221: Clinical Presentation of Afibrinogenemia / Hypofibrinogenemia

Patients With Inherited Severe Fibrinogen Deficiency (n=72)

- Hemarthrosis: 25
- Muscle Hematoma: 17
- Gastrointestinal: 17
- Epistaxis: 10
- Menorrhagia: 7
- Intracranial / Intra / retroperitoneal hemorrhage: 4

Physician Survey 1221: Hemostatic Efficacy

Bleeds:
- Fibrinogen Concentrates: 92%
- Cryo: 94%

Surgeries:
- Fibrinogen Concentrates: 98%
- Cryo: 96%

Traumas:
- Fibrinogen Concentrates: 97%
- Cryo: 91%
Physician Survey 1221: Diagnostic Levels and Treatment Targets for Dosing

Median Plasma Fibrinogen Level (mg/dL)

Differentiation between severe and moderate / mild hypofibrinogenemia
Physician Survey 1221: Diagnostic Levels and Treatment Targets for Dosing

Median Plasma Fibrinogen Level (mg/dL)

“On-demand” treatment for minor bleeding events, routine prophylaxis and prophylaxis for minor events (to be maintained for 1–7 days)
Physician Survey 1221: Diagnostic Levels and Treatment Targets for Dosing

Median Plasma Fibrinogen Level (mg/dL)

0  50  100  150  200

“On-demand” treatment for major bleeding events and prophylaxis for major events (to be maintained for 4–14 days)
Physician Survey 1221: Methods of Fibrinogen Testing

<table>
<thead>
<tr>
<th>Method</th>
<th>% of Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clauss assay</td>
<td>81</td>
</tr>
<tr>
<td>ELISA</td>
<td>19</td>
</tr>
</tbody>
</table>

ELISA=enzyme-linked immunosorbent assay.
Pivotal Study 2001
PK / Efficacy Results
Pivotal Study 2001: Objectives

- **Primary objectives**
  - Single-dose PK analysis
  - Compare MCF before and after administration of FC
  - Demonstrate that MCF 1 hour after FC administration is significantly higher than at baseline

- **Secondary objective**
  - Safety
Rationale for Use of MCF

Clauss assay
- Standard measure for fibrinogen level
- Correlates with ELISA antigen assay

MCF
- Physical measure of the structural integrity of a clot
- Correlates with Clauss assay
- Effectively used in a variety of clinical settings
- Likely to correlate with hemostasis
Rotational Thromboelastometry (ROTEM®)

Detection Principle

- Rotating axis
- Light source
- Digital detection
- Computer software

- Ball Bearing
- Spring
- Pin
- Cuvette with plasma / blood
- Fibrin

CC-33
### Determination of MCF in Plasma

<table>
<thead>
<tr>
<th>Clotting Time (CT / r) [sec]</th>
<th>Clot Formation Time (CFT / k) [sec]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mm</td>
<td>0 mm</td>
</tr>
</tbody>
</table>

#### Firmness vs. Time
- **Firmness**
  - Minimum: 0 mm
  - Maximum: 20 mm

#### Time
- Minimum: 10 min
- Maximum: 20 min

**Maximum Clot Firmness (MCF) [mm]**
Effect of Fibrinogen on MCF as Measured in Plasma

Healthy (MCF=22 mm)

Fibrinogen Deficiency (MCF=ND)

<table>
<thead>
<tr>
<th>EXTEM</th>
<th>Date</th>
<th>Time</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2008-11-14</td>
<td>12:31</td>
<td>2: normal plasma</td>
</tr>
<tr>
<td>CT:</td>
<td>47s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFT:</td>
<td>470s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCF:</td>
<td>22mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α:</td>
<td>80°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A30:</td>
<td>22mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5:</td>
<td>19mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXTEM</th>
<th>Date</th>
<th>Time</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2008-11-14</td>
<td>12:06</td>
<td>2: Fibrinogen deficient plasma</td>
</tr>
<tr>
<td>CT:</td>
<td>1961s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFT:</td>
<td>- s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCF:</td>
<td>- mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α:</td>
<td>- °</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A30:</td>
<td>- mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5:</td>
<td>- mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ND=not detectable.
Comparison of ELISA, Clauss Assay, and ROTEM® Methods in the Assessment of Exogenous Fibrinogen Added to Plasma Samples

Rationale for MCF: Structural Integrity of Clot Is Prerequisite for Stopping Bleeding

Platelet Activation

Platelet Activation

Thrombin Generation

Clot Formation

Clot Lysis

Standard Coagulation Tests

ROTEM® / TEG®
ROTEM® Is Utilized in Several Clinical Settings

- Liver transplantation
- Reduced MCF was associated with increased drainage after cardiac surgery\(^1\)
- Guiding blood product replacement therapy\(^2,3\)
- Predicting risk of bleeding in trauma patients\(^4\)
- Managing postpartum hemorrhage\(^5\)

Prospective, Open-Label, Uncontrolled, Multicenter Study in Patients With Congenital Afibrinogenemiation (N=15)

Single-Dose Infusion of FC (70 mg/kg b.w.)

<table>
<thead>
<tr>
<th>Time Post-Infusion (h)</th>
<th>MCF</th>
<th>Fibrinogen antigen</th>
<th>Fibrinogen activity</th>
<th>Virus safetya</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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<tr>
<td>4</td>
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<tr>
<td>8</td>
<td></td>
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<tr>
<td>24</td>
<td></td>
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<tr>
<td>48</td>
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<tr>
<td>96</td>
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<td>144</td>
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<td>216</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>312</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT FOLLOW-UP

a One additional virus safety follow-up assessment.

BL=baseline; b.w.=body weight; INF=infusion.
Pivotal Study 2001: Major Inclusion and Exclusion Criteria

**Inclusion**
- Congenital afibrinogenemia
  - Fibrinogen activity and antigen <20 mg/dL at screening
  - Age ≥6 years

**Exclusion**
- Acute bleeding
- Planned major surgery needing blood transfusion
- Thromboembolic events within 1 year prior to enrollment
- Other bleeding disorders
- Administration of any fibrinogen-containing product within 2 weeks prior to enrollment
Pivotal Study 2001: Demographics and Baseline Characteristics

15 patients at 10 centers

- 5 females; 10 males
- 4 patients <16 years of age
- 11 patients 16–61 years of age
Pivotal Study 2001: Fibrinogen Activity Levels in Plasma Over Time (PP Population)

Plasma Activity (mg/dL) [Mean ± SD]

Time Post-Infusion (h)

PP=per protocol; SD=standard deviation.

Detection limit for Clauss assay <20 mg/dL.
## Pivotal Study 2001: Pharmacokinetic Results

**PK-PP Population (N=14)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen activity (Clauss assay)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C_{\text{max}}) (mg/dL)</td>
<td>140 ± 27</td>
<td>130 (100–210)</td>
</tr>
<tr>
<td>(t_{1/2}) (h)</td>
<td>78.7 ± 18.13</td>
<td>77.1 (55.73–117.26)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>92.8 ± 20.11</td>
<td>85.9 (66.14–126.44)</td>
</tr>
</tbody>
</table>

MRT=mean residence time.
Pivotal Study 2001: *In Vivo* Recovery of Fibrinogen
PK-PP Population

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibrinogen antigen (ELISA)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase per mg/kg b.w. (mg/dL)</td>
<td>1.7 ± 0.31</td>
<td>1.7 (1.28–2.45)</td>
</tr>
<tr>
<td><strong>Fibrinogen activity (Clauss assay)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase per mg/kg b.w. (mg/dL)</td>
<td>1.8 ± 0.35</td>
<td>1.7 (1.3–2.73)</td>
</tr>
</tbody>
</table>
Pivotal Study 2001: MCF (Primary End Point)

**MCF (mm) [Mean ± SD]**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Infusion (N=13) PP Population</th>
<th>Post-Infusion (1 h) (N=13) PP Population</th>
<th>Post-Infusion (1 h) (N=15a) ITT Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>0 ± 0</td>
<td>10.3 ± 2.7</td>
<td>8.9 ± 4.4*</td>
</tr>
</tbody>
</table>

All results in plasma.

* 2-sided $p$-value from one-sample t-test.

* Only non-missing data are shown (ie, imputed changes due to missing MCFs are not shown).

ITT=intent-to-treat; MCF=maximum clot firmness; PP=per protocol; SD=standard deviation.
**Pivotal Study 2001: Fibrinogen and MCF Results**

**Fibrinogen Activity**

- Normal Range: 180–350 mg/dL
- Minimum Target Level
- Pre-Infusion\(^a\) (N=14, PK-PP)
- 1-h Post-Infusion (N=13, PK-PP)

**MCF**

- Normal Range: 14–30 mm
- Pre-Infusion (N=13, PP)
- 1-h Post-Infusion (N=13, PP)

All results in plasma.
\(^a\) Values <20 mg/dL.

MCF=maximum clot firmness; PK=pharmacokinetic; PP=per protocol.
Study 3001: Objectives

- Demonstrate clinical hemostatic efficacy of FC in the control of acute bleeding in congenital afibrinogenemia
  - Non-inferiority as compared with historical control cryoprecipitate data collected in physician survey 1221

- Correlation between MCF and hemostatic efficacy
Study 3001: Design

Prospective, Open-Label, Historically Controlled Study in Patients With Congenital Fibrinogen Deficiency and Acute Bleeding

Study Arms

- Retrospective (n=39)
- Prospective (n=23)

Treatment Duration

- Day 1 (h): 1, 3, 6, 12, 24
- Pre: Daily (h)
- Post Final Inf (h): 24

Hemostatic efficacy

MCF

Plasma fibrinogen

Treatment duration: minimum 3 days (minor bleeds) to 7 days (major bleeds)

\[ a \] 24 hours after last infusion or day 14 (whichever is earlier).

Virus safety will be assessed at days 10 and 45.
<table>
<thead>
<tr>
<th>Target Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor events: 100 mg/dL for 3 days</td>
</tr>
<tr>
<td>Major events: 150 mg/dL for 7 days</td>
</tr>
</tbody>
</table>

**Dose of fibrinogen** = \((\text{target level} \ [\text{mg/dL}] - \text{measured level} \ [\text{mg/dL}])\) \(1.7^a\) (mg/dL per mg/kg b.w.)

\(^a\) Median *in vivo* recovery taken from pivotal study 2001.
Study 3001: Correlation Between MCF (Surrogate End Point) and Clinical Efficacy

Correlation between MCF and hemostatic efficacy will be estimated in two ways using Spearman’s correlation

- Correlation between absolute MCF values and the clinical outcome assessed on a 4-point hemostatic efficacy scale (excellent, good, poor, none)
- Correlation between change from baseline in MCF and clinical outcome assessed on a 4-point hemostatic efficacy scale (excellent, good, poor, none)
Safety
## Non-Serious Adverse Events

### Congenital Deficiency

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (mg/kg)</th>
<th>Patients with ≥1 AE</th>
<th>Patients with ≥1 possibly treatment-related AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 2001</td>
<td>70</td>
<td>2 epistaxis, GERD, headache, pain</td>
<td>0</td>
</tr>
<tr>
<td>(N=15)</td>
<td>70</td>
<td>4 dyspnea, ↑ temp., injection-site pain, headache, dizziness, nausea</td>
<td>0</td>
</tr>
<tr>
<td>15 Doses</td>
<td>64 (“on demand”)</td>
<td>77 (prophylactic)</td>
<td>36–87</td>
</tr>
<tr>
<td>(2007–2008)</td>
<td>77</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Study 101</td>
<td>70</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(N=6)</td>
<td>77</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6 Doses</td>
<td>77</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(1993)</td>
<td>77</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Study 501</td>
<td>64</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(N=12)</td>
<td>77</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>151 Doses</td>
<td>77</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(1985–1992)</td>
<td>77</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Study 402</td>
<td>36–87</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(N=6)</td>
<td>36–87</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>72 Doses</td>
<td>36–87</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(1985–1987)</td>
<td>36–87</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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*a No information on causal relation of AE to study drug in clinical study report.
Serious Adverse Events (SAEs)

- **Study 501** (N=12; 151 doses): 2 SAEs
  - **Report 1**: Apparent anaphylaxis following dose 56; patient tolerated doses 57–87 without AE
  - **Report 2**: Non-fatal pulmonary embolism
    - Internal fixation surgery of femur fracture
    - Patient treated with a total of 6 doses of FC
    - Dose 6 given in the presence of a DVT
    - Subsequent non-fatal PE 19 days after last dose

- **No SAEs** in other trials for congenital deficiency

DVT=deep vein thrombosis; PE=pulmonary embolism.
Post-Marketing Safety:
Internal Pharmacovigilance Data

- Based on data collected by our post-marketing surveillance system
- ~1 million grams have been distributed
  - Estimated dose per patient per episode ranged from 1 to 8 g, depending on the degree of bleeding
- Post-marketing surveillance from January 1986 to October 2008 resulted in safety reports from 49 patients
AEs and Laboratory Findings of Special Interest
Virus Safety

- Results of virus-validation studies of the manufacturing process, clinical trials, and post-marketing studies consistently demonstrate the safety of FC with regard to virus transmission.

- Two clinical trials evaluated virus safety:
  - No confirmed virus transmission was observed.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Dose</th>
<th>Study Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>15</td>
<td>1</td>
<td>45 to 90 days</td>
</tr>
<tr>
<td>402</td>
<td>6</td>
<td>72</td>
<td>9 months</td>
</tr>
</tbody>
</table>
Virus Safety Post-Marketing Data

14 patients reported positive for hepatitis (no HIV)

- 13 received cellular blood components
- 1 baseline status unknown; timing of hepatitis positivity not consistent with FC as cause
Markers of Coagulation Activation D-Dimer
Study 2001 (N=14)

D-Dimer (µg/L) [Median, Q_{25}-Q_{75}]

Normal Range: <130 µg/L

Pre-Infusion  | 0.5 | 1.0 | 2.0 | 4.0 | 8.0 | Last available data
Time Post-Infusion (h)
Markers of Coagulation Activation Prothrombin Fragment F1+2

Study 2001

F1+2 (nmol/L) [Median, Q_{25–Q_{75}}]

ULN: 0.229 nmol/L

LLN: 0.069 nmol/L

Pre-Infusion 0.5 1.0 2.0 4.0 8.0 Last available data

Time Post-Infusion (h)

LLN=lower limit of normal; ULN=upper limit of normal.
Thromboembolic (TE) Events

- Only one event in clinical trials of FC (previously presented)

- 9 reports in 22 years of post-marketing surveillance
  - 8 Congenital / 1 Acquired deficiency

- Retrospective physician survey 1221 was not designed to collect safety data; TE events reported in:
  - 1 cryoprecipitate-treated patient
  - 2 FC-treated patients
    - Both FC patients had treatment continued at a lower dose
In most of the cases, additional risk factors provided alternative explanations
- Concomitant treatment with other coagulation factors or drugs that may increase thrombotic risk (3 cases)
- Higher baseline risk of thrombosis due to their congenital deficiency (8 cases)

None of the TE events resulted in death
Hypersensitivity Events

In clinical trials:
- One event classified as anaphylaxis following dose 56 in a patient receiving prophylaxis for congenital fibrinogen deficiency
- 30 subsequent doses were tolerated without event

In post-marketing surveillance:
- 6/20 cases met standard diagnostic criteria for anaphylaxis
- 6/20 cases were limited to chills and/or fever

Safety Conclusions

Safety profile of FC is favorable

- Clinical trial AEs were few and generally mild
- No cases of virus seroconversion
- Post-marketing surveillance during 22 years (reflecting ~1 million grams distributed) supports the favorable safety profile of FC
Clinical Perspective

Marilyn Manco-Johnson, MD
Professor of Pediatrics
Director, Hemophilia and Thrombosis Center
University of Colorado Denver
Case 1: Clinical Presentation

- 2-day-old term male; born to G1 mom
- Bleeding from circumcision
- Hgb dropped from 22.7 to 19.7 g/dL
- Also bleeding from heel-stick

Hgb=hemoglobin.
Case 1: Laboratory Evaluation

- **PT**: 85 sec
- **PTT**: >150 sec
- **Plt**: 211,000 / mm$^3$
- **WBC**: 8800 / µL
- **Bilirubin**: 14.8 mg/dL
- **Hgb**: 19.7 g/dL
- **Blood type**: O+
- **Coombs**: Negative

Plt=platelet (count); PT=prothrombin time; WBC=white blood cell (count).
### Case 1: Coagulation Factor Assays

<table>
<thead>
<tr>
<th>Factor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII</td>
<td>120%</td>
</tr>
<tr>
<td>Factor IX</td>
<td>50%</td>
</tr>
<tr>
<td>Factor X</td>
<td>80%</td>
</tr>
<tr>
<td>Factor V</td>
<td>110%</td>
</tr>
<tr>
<td>Factor VII</td>
<td>100%</td>
</tr>
<tr>
<td>Factor II</td>
<td>44%</td>
</tr>
</tbody>
</table>

**Fibrinogen (Clauss assay)**
- $<50$ mg/dL
Case 1: Treatment

- Cryoprecipitate
- Bleeding resolved
- Discharged at age 13 days
Case 1: Clinical Course

- Recurrent muscle, joint, and soft-tissue hemorrhage
- Treated with cryoprecipitate, solvent detergent–treated plasma
- Chronic headaches
- Age 15 years in 2002; began with arterial occlusive lesions of hands and feet following cryoprecipitate or plasma (lasting for weeks following infusions)
- Necrotic infarction of tips of toes and fingers
- Severe pain, requiring chronic narcotics
- Digital lesions failed to respond to steroids, plasmapheresis, immunosuppressive therapy
Case 1: Arterial Occlusions With Afibrinogenemia
Case 1: Laboratory Evaluation

- Plasma sent to 2 research laboratories
- No conclusive evidence for fibrinogen antibody or immune complexes
Case 1: Continued Course

- Patient developed a massive left anterior descending myocardial infarction not related to fibrinogen replacement

- After 1 year in a convalescent hospital, was discharged home
Case 1: Clinical Course

- **Age 20:** developed a headache
  - Went to bed
  - Found dead 20 minutes later

- **Post mortem**
  - Subarachnoid hemorrhage
  - Right frontal parenchymal hemorrhage
  - Bilateral renal arteriolosclerosis
  - Cardiomegaly and left ventricular hypertrophy
Case 2: Clinical Presentation

- 17-month-old female
- Presented with diffuse hematomas of scalp and trunk
- Suspected non-accidental trauma
- Evaluation revealed afibrinogenemia; fibrinogen <10 mg/dL
- PMH compatible with muscle hematoma following 4-month DT immunization

DT=diphtheria-tetanus; PMH=previous medical history.
Case 2: Clinical Course

- Recurrent knee hemarthroses by age 5 years; also hip hemarthroses
- Oozing with tooth eruptions
- Mild menorrhagia starting at puberty
Case 2: Clinical Course (Cont’d)

- Age 14: developed allergic reactions to plasma proteins and cryoprecipitate, resulting in hives and bronchospasm
- Required steroids and Benadryl® pre-treatment and hospital observation for cryoprecipitate
- Age 16: Treated with FC (personal importation) “on demand”
  - Approximately monthly for soft tissue, muscle, and joint hemorrhages
- Full-time university student pursuing a career as a nurse practitioner
Risk of TE Complications Is Increased in Congenital Fibrinogen Deficiency

- Certain patients have a higher intrinsic risk of TE events independent of treatment
- Fibrinogen replacement is frequently required in high-risk situations
- Increased risk is not product specific—plasma and cryoprecipitate have the same association with TE events
- Treating physicians should be acutely aware of a delicate balance: high clinical suspicion and monitoring are needed
Hypersensitivity

- Patients with chronic exposure to plasma and cryoprecipitate often develop reactions to plasma proteins

- Reports of FC-related events are uncommon
  - 20 out of ~1 million grams in 22 years of use
Fibrinogen Concentrate Benefits

- Proven ability to consistently raise fibrinogen concentration to hemostatic levels and promote clot formation
  - Minimizes debilitating and fatal bleeding complications in patients with congenital deficiencies
  - Works in a disorder that ranges from life-threatening to chronic, recurrent to rare bleeding

- Supported by 22 years of clinical experience in treating or preventing bleeding in these patients
Heat Treated Fibrinogen Concentrate: Improvement Over Current Therapy

- Precise dosing
- Fewer extraneous proteins
- Validated virus inactivation
- Smaller volume
- Rapid preparation
- Inventory