SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Pathogen Reduction System for Plasma

Device Trade Name: INTERCEPT® Blood System for Plasma

Device Procode: PJF

Applicant's Name and Address: Cerus Corporation
2550 Stanwell Drive
Concord, CA 94520

Date(s) of Panel Recommendation: N/A

Premarket Approval Application (PMA) Number: BP130076

Office's Signatory Authority: Ginette Michaud, MD for
Jay S. Epstein, MD
Director, OBRR/CBER

□ **I concur with the summary review.**

□ **I concur with the summary review and include a separate review to add further analysis.**

□ **I do not concur with the summary review and include a separate review.**

Date of FDA Notice of Approval: December 16, 2014

II. INTENDED USE

The INTERCEPT Blood System (IBS) for Plasma is intended to be used for *ex vivo* preparation of pathogen-reduced, whole blood derived or apheresis plasma in order to reduce the risk of transfusion transmitted infection (TTI).

III. CONTRAINDICATIONS

- Contraindicated for preparation of plasma intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.
- Contraindicated for preparation of plasma intended for neonatal patients treated with phototherapy devices that emit wavelengths less than 425 nm due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

IV. WARNINGS AND PRECAUTIONS

Only INTERCEPT Processing Sets for plasma are approved for use in IBS. Use only the INT100 Illuminator for ultraviolet light (UVA) illumination of amotosalen-treated plasma. No other source of UVA light may be used. Please refer to the Operator's Manual for the INT100 Illuminator. Discard any plasma not exposed to the complete INT100 illumination process.

Tubing components and container ports of the INTERCEPT Blood System contain polyvinyl chloride (PVC). Di(2-ethylhexyl)phthalate (DEHP) is known to be released from PVC medical devices, and increased leaching can occur with extended storage or increased surface area contact. Blood components will be in contact with PVC for a brief period of time (approx. 15 minutes) during processing. The risks associated with DEHP released to into the blood components must be weighed against the benefits of therapeutic transfusion.

Cardiac events

In a randomized controlled trial of therapeutic plasma exchange (TPE) for TTP, five patients treated with IBS processed plasma had reported adverse events in the cardiac system organ class (SOC) versus none with conventional plasma. These events included: angina pectoris (n=3), cardiac arrest (n=1), bradycardia (n=1), tachycardia (n=1) and sinus arrhythmia (n=1). None of these events resulted in documented myocardial infarction or death. Monitor patients for signs and symptoms of cardiac events during TPE for TTP.

V. DEVICE DESCRIPTION

The IBS for Plasma contains a sterile, non-pyrogenic, single use, integrated, fluid path plasma processing set (INT3110) comprised of four key components (see table below) and a UVA illumination device (INT100) for the *ex vivo* preparation and storage of pathogen-reduced, whole blood-derived or apheresis plasma. The INT100 is a microprocessor-controlled device designed to deliver a controlled amount of UVA light, wavelength 320 – 400 nm and may accommodate up to two illumination containers simultaneously. The

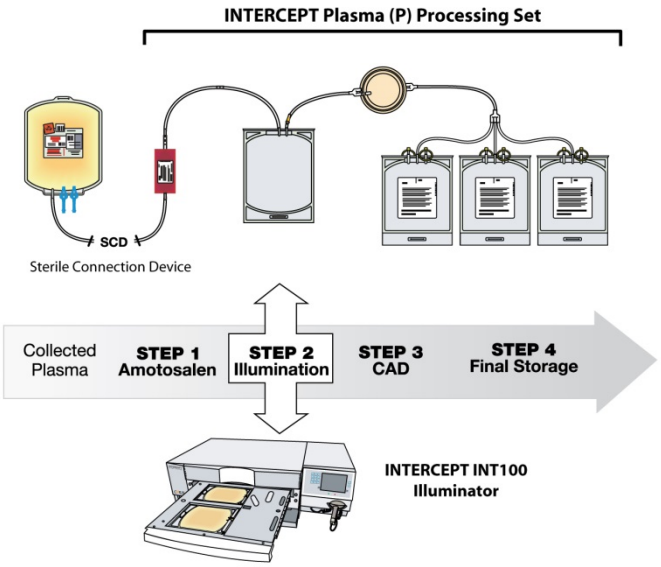
device is programmed to control, deliver, record and store intensity and duration of light dose for each cycle.

Components of the INTERCEPT Plasma Processing Set (INT3110)

Component	Description
Amotosalen (S-59, psoralen derivative) solution container	15 mL, 6 mM amotosalen in 0.924% NaCl packaged in a 20 mL, flexible, heat sealed plastic container, with an integral light-protective overwrap and sleeve
Illumination container	Heat sealed, plastic bag
Compound Adsorption Device (CAD)	Ground beads and binder in a sintered disk contained within ultrasonically welded housing
Plasma storage containers	Three plasma bags, ~400 mL storage capacity

The operating principle for the IBS for Plasma is illustrated in the figure below.

Illustration of the IBS for Plasma



Whole blood derived or apheresis plasma in a container is sterile connected to the INT3110 plasma processing set. The plasma flows through the amotosalen container into the illumination container. The illumination container is placed into the INT100 illumination device for UVA treatment while being mixed with horizontal agitation. Inactivation of potential pathogen or leukocyte contaminants in plasma is achieved through a photochemical treatment process in which amotosalen (S-59, psoralen derivative), a chemical capable of binding to nucleic acids, is added to the plasma and UVA illumination (320 – 400 nm wavelength) of the amotosalen-treated plasma induces covalent cross-linking of any nucleic acids to which amotosalen is bound; thereby, preventing further replication. Treated plasma is then passed through the compound adsorption device (CAD) to remove unreacted amotosalen and free photoproducts (b)(4)----------. Finally, the plasma is distributed among two or three plasma bags

for use or storage at or below -18 ^{o}C. Processed plasma must be placed in a -18 ^{o}C freezer within 24 hours of blood draw for pooled whole blood derived plasma or within 8 hours of apheresis collection

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no alternate pathogen reduction devices for plasma approved in the U.S. There are alternative therapies available for patients requiring therapeutic plasma transfusion or exchange, some of which have been manufactured with pathogen inactivation processes. These products include:

- Fresh Frozen Plasma (FFP)
- OCTAPLAS, Pooled Plasma (Human), Solvent/Detergent Treated
- PF24 - plasma frozen within 24 hours after phlebotomy
- PF24RT24 - plasma held at room temperature then frozen within 24 hours after phlebotomy.

Competitor Pathogen Inactivation Products

There are no competitor pathogen inactivation devices.

VII. MARKETING HISTORY

The IBS for Plasma device was CE marked in 2006 and is commercially available in the following countries:

Belgium	Germany	Liechtenstein	Romania
Bosnia	Greece	Lithuania	Russia
Chile	Hungary	Luxembourg	Slovakia
Cyprus	Iceland	Malta	Slovenia
Czech Republic	Ireland	Netherlands	Spain
Denmark	Israel	Norway	Sweden
Estonia	Italy	Poland	Switzerland
Finland	Kazakhstan	Portugal	Turkey
France (including La Reunion, Martinique, Guadeloupe, Tahiti)	Latvia	Qatar	Ukraine
United Kingdom			

VIII. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1. Field Studies

REL-R-00428: *In vitro* Study of Whole Blood Derived Plasma Prepared with the INTERCEPT Blood System

Study method: This study was conducted at two blood centers. Test samples were derived from whole blood plasma, which was processed and frozen within 24 hours. Sixty two pools, (186 total units) of plasma were collected. A portion of each pool was separated, frozen and tested as the untreated control. The remaining portion of each pool was processed using the INTERCEPT system, frozen, and then tested in parallel with untreated control samples. A summary of study results is presented in the table below.

***In Vitro* Study Results**

Test	IBS processed plasma		Control plasma	
	Mean±SD	Range	Mean±SD	Range
pH	7.38±0.03	7.35 – 7.45	7.41±0.05	7.34 – 7.58
Osmolality (mOsm/kg)	308±5	294 –321	309±5	295 – 322
PT (s)	14.4±0.7	12.7 – 16.9	13.1±0.7	11.6 – 15.3
aPTT (s)	27.0±1.7	23.1 – 31.3	24.2±1.4	20.4 – 27.6
Fibrinogen (g/L)	2.43±0.37	1.70 – 3.74	2.91±0.36	2.28 – 4.10
Prothrombin (IU/mL)	0.93±0.09	0.72 – 1.14	1.03±0.10	0.85 – 1.28
Factor V (IU/mL)	0.82±0.11	0.51 – 1.19	0.91±0.13	0.56 – 1.27
Factor VII (IU/mL)	0.81±0.13	0.60 – 1.22	0.99±0.14	0.71 – 1.41
Factor VIII (IU/mL)	0.73±0.20	0.35 – 1.21	0.91±0.25	0.44 – 1.52
Factor IX (IU/mL)	0.93±0.17	0.58 – 1.56	1.12±0.19	0.71 – 1.66
Factor X (IU/mL)	0.83±0.13	0.53 – 1.18	0.95±0.14	0.62 – 1.33
Factor XI (IU/mL)	0.90±0.13	0.66 – 1.28	1.02±0.14	0.77 – 1.43
vWF R:Co (IU/mL)	0.97±0.24	0.46 – 1.55	1.01±0.25	0.51 – 1.56
ADAMTS-13 antigen (%)	128.8±20.6	94.0 – 181.4	124.7±17.9	90.4 – 173.4
ADAMTS-13 activity (%)	87.5±11.0	64.0 – 114.8	93.4±10.3	68.0 – 114.8
Antithrombin III (IU/mL)	0.93±0.06	0.73 – 1.07	0.98±0.06	0.76 – 1.11
Protein C (IU/mL)	0.86±0.09	0.67 – 1.01	0.95±0.10	0.79 – 1.20
Protein S (IU/mL)	1.04±0.10	0.84 – 1.26	1.08±0.11	0.84 – 1.30
Alpha-2-plasmin Inhibitor (IU/mL)	0.85±0.07	0.63 – 1.02	1.00±0.08	0.72 – 1.18
TAT (IU/mL)	2.3±0.8	2.0 – 6.3	2.4±0.8	2.0 – 6.7
Factor VIIa (ng/mL)	<3.6	<3.6	<3.6	<3.6
NAPTT (s)	91.8±11.4	70.3 – 121.9	91.8±10.6	69.9 – 118.4
C3a (ng/mL)	50.4±38.4	13.0 – 216.2	134.7±57.0	66.8 – 359.0

REL-R-00429: *In vitro* Study of Apheresis Plasma Prepared with the INTERCEPT Blood System

Study method: This study was similar in design and execution to REL-R 00428. Apheresis plasma was the starting material. The study results were similar to those presented for whole blood derived plasma.

Conclusion

In vitro study results indicated comparable levels in IBS vs. untreated plasma for the majority of plasma proteins studied. For IBS processed plasma there were observed decreases in levels of Factor VIII and Fibrinogen and prolongation of PT and aPTT. The *in vitro* differences did not appear to impact clinical outcomes in studies supporting the indications for use for IBS processed plasma.

2. Pathogen Reduction Studies

The IBS reduces activity of certain enveloped viruses, gram-positive and gram-negative bacteria, spirochetes, parasites and leukocytes. There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses [(e.g., hepatitis A virus (HAV), hepatitis E virus (HEV) and poliovirus] and *Bacillus cereus* spores have demonstrated resistance to the IBS process. A number of independent *in vitro* studies evaluated the capability of the IBS process to reduce infectivity of pathogens relevant to transfusion transmitted infections. A summary of pathogen reduction study results is presented in the table below.

Summary of Pathogen Reduction Study Results

Pathogen	Log Reduction
Virus (Enveloped)	
HIV-1 IIIB, cell-associated	≥6.2
HIV-I IIIB cell-free	≥6.1
DHBV	4.4 to 4.5
BVDV (model for HCV)	≥4.5
HTLV-I	≥4.1
HTLV-II	≥4.7
West Nile virus	≥6.7
SARS-Associated Coronavirus	≥4.0
Chikungunya virus (CHIKV)	6.5
Influenza A virus (H_5N_1 Avian Influenza)	≥5.7
Virus (Non-Enveloped)	
Parvovirus B19	1.8
Bluetongue virus	≥4.0
Adenovirus 5	≥5.6
Bacteria	
Klebsiella pneumoniae	≥6.7
Yersinia enterocolitica	≥6.6
Staphylococcus epidermidis	≥6.6
Treponema pallidum	≥5.4
Borrelia burgdorferi	≥9.9
Anaplasma phagocytophilum (HGE agent)	≥3.6
Protozoan Parasite	
Plasmodium falciparum	≥5.9
Babesia microti	≥4.9
Trypanosoma cruzi	>5.0

The IBS process demonstrated a reduction factor of 4 $\log_{10}$ for viable T cells, as assessed using a limiting dilution assay.

3. Stability Studies

a. INTERCEPT Processing Set Stability

Cerus seeks to obtain a shelf-life of (b)(4) months for INTERCEPT processing sets when stored at (b)(4) – 25 ^{o}C. Several stability studies have been conducted to support the intended shelf-life. Studies PRD-00229, SUD-00698-2 and SUD-00620 were completed on lots produced in 2005 for CE mark registration, and provided (b)(4) months of long-term and (b)(4) months of accelerated stability data, which supported the claimed shelf-life. Ongoing stability studies on more recent lots are being performed. Interim study reports, PRD-00182-3, PRD-00197-2, PRD-00223-1 provided data from amotosalen solution stability monitoring, CAD functional testing and plasma bag UV transmission measurements. Results from monitoring amotosalen dose and degradation products as a function of storage temperature and time were recorded. Interim stability data revealed trends in amotosalen dose that reflected ----------(b)(4)----------. Interim stability data indicated acceptable stability for up to (b)(4) months, at temperatures up to 25 ^{o}C. Temperatures above 25 ^{o}C, however, negatively impacted amotosalen stability; therefore, the product will be labeled, "Do not store above 25 ^{o}C."

Cerus and -(b)(4)- have established an -(b)(4)- stability monitoring program to monitor ongoing processing set stability and to qualify manufacturing changes. The stability specification for the amotosalen solution container includes tests for amotosalen dose, amotosalen assay, (b)(4), impurities and microbial safety. Photostability studies supported storage and handling conditions for the amotosalen solution in its container closure, -(b)(4)- plastic container with integral ----(b)(4)---- ---------- sleeve with label. Cerus has committed to conducting prospective stability studies to confirm stability of the intended U.S. commercial configuration of assembled processing sets. Study PRD-00235 will monitor amotosalen solution stability and study PRD-00218 will monitor the processing set dry side. Cerus committed to completing each (b)(4) month study.

b. INTERCEPT Plasma Stability

Long-term stability of frozen plasma units is being supported by ongoing studies, REL-IR1-00438 and REL-IR1-00439. REL-IR1-00439 reported 3 month stability data for (b)(4) samples of IBS whole blood derived plasma characterized in study report REL-R-00428 (see above). REL-IR1 00438 reported 3 month stability data for (b)(4) samples of IBS apheresis plasma characterized in study report REL-R 00429 (see above). All parameters tested at release are being monitored on stability. Stability time points are planned at 3, 6, 12, and (b)(4) months to support a 12 month shelf-life when stored at or below -18 ^{o}C. Interim stability data demonstrated acceptable 3 month stability for all parameters tested.

B. <u>Animal Studies of Amotosalen Toxicity</u>

Nonclinical studies were conducted in mice, rats and dogs to evaluate the potential toxicity of single and repeated exposures to amotosalen, the synthetic psoralen derivative used in the IBS to cross-link DNA and RNA. A single, intravenous injection of amotosalen alone resulted in mortality in rats at doses equal to or greater than 35,000-fold

the anticipated human exposure from IBS processed plasma, on a dose per kilogram body weight basis. Lower doses (4,000- or 20,000-fold greater than the human exposure in dogs and rats, respectively) were not lethal, and resulted in transient clinical signs of toxicity (i.e. piloerection, inactivity, hunched posture and abnormal breathing in rats, and excessive salivation, convulsions, and non-lethal cardiac arrhythmias in dogs). No target organ toxicities were noted at necropsy.

Animal experiments provided no indication of an increased toxicological risk for the use of IBS processed plasma using the IBS. Single dose studies with IBS processed plasma in dogs were non-toxic at amotosalen doses of 6,000-fold the expected clinical exposure, and repeated daily dosing in rats and dogs for 28 days with homologous plasma processed with the IBS showed no evidence of toxicity at 5,000-fold the expected amotosalen clinical exposure.

Amotosalen was rapidly eliminated following intravenous dosing in mice and rats, with an initial plasma $t_{½}$ of less than one hour. There was no evidence of amotosalen accumulation after repeated exposures over periods as long as 13 weeks. The primary route of excretion of amotosalen and its photo-byproducts was fecal.

No effects on fertility parameters were noted in male or female rats repeatedly dosed with amotosalen. In studies evaluating the effects of amotosalen dosing of pregnant rats or rabbits on embryo-fetal or peri-postnatal development, and in one study of neonatal rats dosed with amotosalen or homologous IBS processed plasma, there was no evidence of teratogenicity, or other reproductive or developmental toxicities. No evidence of genotoxicity or mutagenicity was observed in the *in vitro* or *in vivo* mutagenicity studies of amotosalen. In transgenic mice heterozygous for the p53 tumor suppressor gene, there was no evidence of carcinogenicity after repeated, three times weekly dosing for 6 months with amotosalen in plasma, at cumulative weekly doses approximately 150 times the human exposure from a single infusion of IBS processed plasma.

C. Additional Studies

Electrical and sterilization studies were performed on the IBS and were noted to be acceptable.

All nonclinical studies conducted with the extractable and leachable components of the IBS met the criteria for passing their specific tests, as outlined in the ISO 10993-(b)(4)---------- standards. There were no adverse findings in *in vitro* cytotoxicity and biocompatibility testing of either the plastics themselves or of aqueous or aliphatic extracts of the storage containers, labels, or the CAD (b)(4) in its container closure system in cytotoxicity studies with (b)(4) cells, hemolysis of ---(b)(4)----whole blood and Ames assay for mutagenicity testing, or in *in vivo* local tolerability in rabbits, dermal sensitization in guinea pigs, and single and repeat-dose intravenous toxicity studies in mice and rats, respectively. Additionally, the same testing performed on ----(b)(4)---------- extracts of the IBS did not result in detectable, treatment-related toxicities in any of the test systems assayed. A comprehensive risk assessment based on the identity, quantity and toxicity of the individual extractable chemicals from the plastic storage containers and the CAD did not reveal significant risk of toxicity,

mutagenicity, carcinogenicity or teratogenicity at the exposure levels present in a predicted human daily dose of 1000 mL IBS processed plasma per day, with safety margins between 125-fold and 130,000-fold between the anticipated human daily exposures and the non-toxic, intravenous dose levels of the individual chemicals.

Cerus adheres to a number of national and international voluntary standards that identify industry recommendations for medical device quality systems, development and manufacturing processes applicable to the IBS for Plasma.

IX. SUMMARY OF PRIMARY CLINICAL STUDIES

The safety and effectiveness of IBS processed plasma were investigated in eight clinical studies summarized in the table below (N=704).

Clinical Trials of IBS Processed Plasma

Trial	Phase	Design	Clinical Setting	N	Objectives
C-001-97	1	Randomized Crossover Blinded	Healthy Subjects	15	Amotosalen kinetics Safety
C-002-97	2	Randomized Crossover Blinded	Anticoagulated Healthy Subjects	27	Warfarin reversal Factor kinetics Safety
C-002-98	2	Randomized Parallel Group Blinded	Acquired Coagulopathy Liver Disease	13	Pilot study Logistics Clinical response
F3A99UC*	3	Single Group Open Label	Congenital Coagulopathy	34	Factor kinetics Clinical response Safety
F3B99	3	Randomized Parallel Group Blinded	Acquired Coagulopathy Liver Disease	121	Clinical response to invasive surgery Safety
F3C99	3	Randomized Parallel Group Blinded	TTP with therapeutic plasma exchange	35	Clinical response Safety
CLI 00080	Post marketing in Europe	Retrospective Cohort Controlled Comparative Efficacy	TTP	31	Clinical response
EFS Alsace/ Strasbourg University	Post marketing in Europe	Retrospective Cohort Controlled Comparative Efficacy	Liver Transplant	427	Clinical response Safety

**Not discussed in detail as the data are not adequate to support the indication*

A. Overview of Efficacy based on Patient Population, Study Design and Efficacy Endpoints

1. Patient Population

The objectives of the clinical development program were to obtain efficacy and safety data on the uses of IBS processed plasma as described in the AABB Circular of Information for the Use of Human Blood and Blood Components[1].

a. Liver Disease (Study F2B99)

Two randomized, prospective, double blind, controlled clinical trials in patients with acquired coagulation deficiencies resulting from acute or chronic liver disease, and one retrospective analysis of data from patients with acute or chronic liver disease undergoing transplant were conducted. In F2B99, patients with acquired coagulopathy associated with liver disease requiring plasma transfusion to support either a major or minor medical procedure (N=121) were evaluated for changes in prothrombin time (PT) and activated partial thromboplastin time (PTT). Fifty-one of the patients in the trial were enrolled for plasma transfusion support associated with orthotopic liver transplantation (OLT).

In the retrospective study, 335 liver transplants were performed in 328 patients with plasma transfusion support. The study examined blood product consumption, treatment differences in fresh frozen plasma (FFP) volume transfused, total platelet dose transfused, and RBC components transfused from the time of surgery through post-operative day 7, as well as safety outcomes, such as hepatic artery thrombosis (HAT) within nine days of transplant and mortality within seven days of transplant. One hundred seventy four transplants were supported with IBS processed plasma in 171 patients, and 161 transplants in 157 patients were supported with conventional FFP.

No clinically relevant differences were detected between the treatment groups in efficacy or safety measures.

b. Thrombotic Thrombocytopenic Purpura (Study F3C99)

A randomized, prospective controlled Study F3C99 (N=35) and one retrospective non-randomized non-interventional cohort study CLI 00080 in patients with thrombotic thrombocytopenic purpura (TTP) requiring therapeutic plasma exchange (N=31) were conducted. In both studies, patients of age 2 years or older were enrolled. Patients were required to have a clinical diagnosis of TTP confirmed by thrombocytopenia (platelet count $<100 \times 10^9$/L) and micro-angiopathic hemolytic anemia. In both studies, patients were excluded if they had recent (within one year) bone marrow or hematopoietic stem cell transplantation, acute or chronic disseminated intravascular coagulation, malignancy, collagen/vascular/autoimmune disease, AIDS, malignant hypertension, or a high serum creatinine value. Consistent

1 Refer to the Circular of Information for the Use of Human Blood and Blood Components at www.aabb.org/aabbcct/coi/Pages/default.aspx

with the higher frequency of TTP reported in females and in Blacks, the TTP population enrolled had a higher proportion of both females and Blacks (M: F 18:82; Blacks: Caucasians 65:35).

2. Study Designs

Studies of IBS processed plasma in liver disease and liver transplantation, or TTP were both prospective and retrospective. Each indication included at least one prospective, well-controlled clinical trial. The size of the TTP studies was limited by the rarity of this condition. The retrospective studies were designed to supplement the efficacy conclusions from the prospective studies as well as to further assess potential safety signals. Thus the retrospective studies, by design, included similar demographics and durations of follow up; all subjects who met the inclusion criteria during the specified study period were included in the studies/analyses, to minimize selection bias.

3. Efficacy Endpoints

Measured parameters, broadly indicative of the effectiveness of IBS processed plasma across multiple therapeutic indications, were assessed either directly or indirectly in the clinical studies, including: increments in specific coagulation factors following transfusion, impact of transfusion on global assays of coagulation activity (PT and PTT), clinical hemostasis, and use of blood components. These parameters were mostly assessed in the prospective studies, although use of blood components was collected in the retrospective studies of subjects undergoing liver transplant and in subjects with TTP.

a. Increments in Coagulation Factors Following Transfusion and Impact of Transfusion on Coagulation Activity (PT and PTT) – Study F3B99

The primary objective of plasma transfusion is to correct abnormal conditions of hemostasis to either prevent or treat bleeding due to coagulopathy arising in a spectrum of clinical disorders. Direct evaluation of hemostasis in patients with active bleeding due to trauma or surgical intervention is difficult due to confounding factors including the heterogeneity of trauma severity and surgical complications not directly reflective of plasma transfusion efficacy. Study F3B99 (N=121) was designed to measure post transfusion coagulation factor specific activity and impact on PT and PTT. Factor VII (FVII) was a focus for evaluation of coagulation factors because this factor has a short half-life, and FVII activity is commonly decreased in patients with coagulopathy of liver disease and liver transplant. Because of its short half-life relative to other coagulation factors and the substantial impact on the PT and INR, which are used commonly to determine FFP dosing frequency, FVII levels are an important efficacy indicator. Change in PT and PTT one hour following the first study transfusion, adjusted for FFP dose and patient weight, was the primary endpoint of Study F3B99 in patients with liver disease and patients undergoing liver transplant.

Incremental recovery of FVII was comparable between test and control groups in patients with acquired coagulation deficiencies. Post-transfusion increments and kinetics of FVII after transfusion of IBS processed plasma and conventional plasma were similar in patients with chronic liver disease undergoing surgical procedures.

Other coagulation factors increments without adjustment for FFP dose or body weight were calculated in Study F3B99 for different coagulation factors. There were no differences seen in the coagulation factor response of patients to IBS processed plasma compared to conventional FFP. There were no differences between treatment groups for the primary endpoints of dose adjusted and unadjusted PT and PTT response to the first study transfusion.

Overall, transfusion of IBS processed plasma resulted in increased coagulation factor specific activity with factor clearance rates similar to those of conventional plasma and consistent with hemostatic efficacy seen with conventional plasma.

b. Clinical Hemostasis

In Study F3B99, hemostatic evaluations using the modified WHO 5-point bleeding scale (refer to Appendix 1) were performed pre- and post-transfusion for all transfusion episodes during the 7-day period of plasma support. Bleeding was assessed for the 8-hour period prior to transfusion through the 8-hour period post-transfusion. Both the incidence of bleeding at each potential bleeding site and an overall hemostatic grade for all bleeding sites, representing the most severe bleeding grade at any site, were determined at each time point. In addition, bleeding identified by the Investigators as clinically significant was recorded as an adverse hemorrhagic event, and graded as mild, moderate or severe.

Treatment groups did not differ in the median change in overall hemostatic grade in the modified intent to treat population for the first transfusion or for subsequent transfusions. Most of the mean values for hemostasis were Grade 1 or less both pre- and post-transfusion. These results are summarized in the table below.

Distribution of Overall (Maximum) Hemostatic Grade Pre- and Post-Transfusion for First Study Transfusion Study F3B99

	Test N=60	**Control N=60***	**p-Value[a]**
Pre-transfusion			
Grade 0	31 (52%)	29 (48%)	0.748
Grade 1	18 (30%)	17 (28%)	
Grade 2	9 (15%)	8 (13%)	
Grade 3	2 (3%)	5 (8%)	
Grade 4	0 (0%)	1 (2%)	
Post-transfusion			
Grade 0	32 (53%)	26 (43%)	0.247
Grade 1	7 (12%)	3 (5%)	
Grade 2	15 (25%)	22 (37%)	
Grade 3	6 (10%)	7 (12%)	
Grade 4	0 (0%)	2 (3%)	

NOTE: Overall hemostatic grade represents the most severe bleeding grade at any site.
** NOTE: One Control OLT patient with missing data*
a. p-Value for treatment difference in distribution from 2-sided Fisher's exact test.

c. Use of Blood Components

One objective measure of the ability of plasma transfusion therapy to provide effective hemostasis is the global use of blood components during a period of transfusion support. This measure generally requires a sufficiently large patient population to minimize the effects of patient heterogeneity between treatment groups supported with conventional or IBS processed plasma. In Study F3B99, the proportion of patients requiring other blood components was higher for the subpopulation undergoing liver transplant, and the mean number of each of these components transfused was likewise higher for this population. However, there were no differences between test and control cohorts for either the liver transplant or the non-transplant subpopulations for any blood component transfused, recognizing that the study was not powered to detect such differences.

In patients with TTP undergoing therapeutic plasma exchange (TPE) treatment, exposure to blood products other than plasma could be indicative of the need to treat acquired coagulopathy or bleeding due to ineffective plasma coagulation function. Each TPE results in replacement of approximately 75% of the recipient's plasma volume. Thus, maintenance of hemostasis is largely due to replaced plasma. Ineffective coagulation function of replacement plasma with repeated TPE could lead to hemostatic failure with increased bleeding and requirement to transfuse more plasma or RBC components. In the prospective study in this population, Study FC399 (N=35) only 2 patients, one in each group, received non-study plasma; and the amounts transfused were limited. Only 2 patients, both in the test group, received a single platelet transfusion. Transfusion of RBC components during TPE in cycle 1 (most patients had only one cycle of treatment) was more frequent, but not different between the treatment groups. In the retrospective study of patients with TTP undergoing TPE treatment (CLI 00080), except for 1 patient in the test cohort who received 3 units of therapeutic plasma, there was a trend for less blood component use in the test cohort. Cumulatively, these data indicate that in those patients supported with large amounts of IBS processed plasma, hemostasis was adequately maintained, recognizing that the study was not powered to detect a difference in the number of RBC or platelet components transfused.

B. Dosing

As noted in the AABB Circular of Information, dosing of FFP depends upon the clinical situation and patient size and may be guided by laboratory assays of coagulation function. FFP is typically dosed at 10-20 mL/kg depending on the clinical indication (Friedman and Menitove 2001, Bucur and Hillyer 2003a). Although there is considerable heterogeneity in the recommended starting exchange volume for TPE treatment of TTP, most centers start with a 1 or 1.5 plasma volume exchange dose (George 2000; Rock et al. 2000; Bandarenko 1998). Guidelines indicate that TPE should be started with 1.5 plasma volume exchanges in all age groups and reassessed daily.

In all prospective clinical trials, IBS processed plasma dosing was comparable to control FFP dosing, and was based on established dosing of conventional FFP. Clinical efficacy of FFP transfusion in all clinical trials was achieved with similar IBS processed plasma and control FFP exposure, in terms of FFP volume, number of FFP units transfused, and

number of FFP transfusion episodes. FVII incremental recovery, a parameter used to guide FFP dosing, was comparable between treatment groups in both the F3B99 and F3C99 trials.

Based on the comparable results when used at similar doses, there is no change in plasma dosing with IBS processed plasma compared to conventional plasma**.**

C. Safety

1. Overview of safety based on overall patient population, specific patient population and clinical situations

During the prospective clinical trials and the post-marketing studies, special consideration was taken to monitor the most important potential safety risks associated with plasma transfusion including acute transfusion reactions including allergic and anaphylactic reactions, and transfusion related acute lung injury (TRALI).

2. Extent of Exposure

The extent of patient exposure to IBS processed plasma has been analyzed by duration and dose for the clinical studies. Duration in days is summarized in the table below.

Exposure by Duration[1] in Days

	C-002-97 and C-002-98		F3A99UC	F3B99		F3C99	
	Test (n=42)	Control (n=42)	Test (n=34)	Test (n=66)	Control (n=68)	Test (n=35)	Control (n=31)
Mean (SD)	1.0 (0)	1.0 (0)	45.6 (98.8)	2.0 (1.8)	2.2 (2.1)	42.5 (133)	50.1 (117)
Median	1.0	1.0	1.0	1.0	1.0	18.0	17.0
Min, max	1, 1	1, 1	1, 428	1, 7	1, 8	1, 802	3, 632

[1] Treatment duration was calculated as: date of last study transfusion – date of first study transfusion +1.

Study#C-002-97 and C-002-98 - anti-coagulated Healthy Subjects Acquired Coagulopathy Liver Disease

F3A99UC Congenital Coagulopathy

F3B99 Acquired Coagulopathy Liver Disease

F3C99 TTP with therapeutic plasma exchange (TPE)

In terms of overall mean doses, in the F3B99 study, the mean dose of IBS processed plasma for all patients was 2.8±3.0 L compared to 3.6±3.6 L for untreated plasma. The mean dose of IBS processed plasma for patients undergoing liver transplant was 4.8±3.7 L compared to 5.2±3.6 L with untreated plasma. In the F3C99 study in TTP patients, the mean volume of IBS processed plasma was 53 L (range 18-138 L).

3. Amotosalen Clearance and Potential Immunogenicity

The preparation of IBS processed plasma involves the use of a synthetic psoralen, amotosalen HCl and UVA light for pathogen inactivation. Although the levels of residual amotosalen are substantially reduced by the compound adsorption device (CAD), small amounts of residual amotosalen are transfused with the treated plasma resulting in patient exposure to amotosalen. Studies were conducted in healthy subjects to measure the clearance of residual amotosalen; and in patients to assess the residual amotosalen

levels as well as the potential for development of an immune response to amotosalen-associated neoantigens.

The clinical trial C-001-97 was conducted to assess tolerability and safety of IBS processed plasma in healthy volunteers. This study was designed as a phase 1, crossover trial, transfusing autologous IBS processed plasma and control (untreated) autologous FFP into single-blinded healthy volunteers (N = 15). Subjects were randomized to dose (100, 200, 400 and 1000 mL) and treatment sequence. All subjects completed both transfusions at one dose before any subjects received the next higher dose.

In the healthy subjects who were exposed to a single transfusion of 1,000 mL of IBS processed plasma, the mean peak concentration of amotosalen was 11.5 ng/mL. The clearance best fit a tri-phasic exponential decay model. The mean plasma amotosalen concentration 16-24 hours after transfusion was 0.52±0.10 ng/mL. The mean AUC and extrapolated AUC were 10.3 and 11 ng/mL, respectively. The mean distribution and terminal half-lives were 3,679.2 mL and 138.5 minutes, respectively. No healthy subjects developed amotosalen-specific antibodies.

In a subsequent trial of IBS processed plasma versus conventional plasma in patients with acquired coagulopathies (Study C-002-98), the immediate post-transfusion amotosalen levels (5.85 ng/mL) were lower than those seen in healthy volunteers (11 ng/mL). However, by 24 hours, the levels were comparable, 0.52 ng/mL in healthy subjects; 0.32 ng/mL in patients with acquired coagulopathies. No patients developed amotosalen-specific antibodies.

4. Common and Non-Serious Adverse Events

a. Randomized Controlled Trials

In the integrated safety analysis of the randomized controlled trials (RCT), the most common adverse events (AEs) were consistent with the frequent and significant AEs that are reported in subjects with acquired coagulopathies undergoing invasive procedures, including liver transplant, as well as the subjects with TTP requiring TPE. Overall, 96% of test patients and 93% of control patients reported at least one treatment-emergent adverse event.

Overall, no AE was reported with significantly greater frequency in the RCT test group compared to the control group. However, three AEs approached statistical significance in the overall analysis: angina pectoris (5% test, 0% control; p=0.056), bradycardia (7% test, 1% control; p=0.061), and white blood cell decreased (0% test, 5.8% control, p= 0.059). The difference in incidence of angina in the test group reflects the higher incidence of cardiac events reported in study F3C99 in subjects with TTP. The difference in incidence of bradycardia reflects the higher number of test subjects reporting this event in study F3B99 (acquired coagulopathies), primarily in the subgroup of patients who underwent liver transplant (OLT). Within the OLT subgroup, 18.2 % of test subjects vs. 3.4% of control subjects experienced an event of bradycardia (p=0.152). The overall number of subjects undergoing OLT who experienced events in the Cardiac Disorders System Organ Class (SOC) was not

different between the test and control groups (12 each; 54.5% and 41.4 %, respectively, p = 0.405).

The most common adverse reactions in the RCT (reported as possibly or probably related to IBS processed plasma and occurring in 2 or more study subjects) included: pruritus (7.2%), urticaria (6%), hypokalemia (4.8%), anemia (3.6%) and nausea (3.6%). Vomiting, pyrexia, rigors, hypomagnesemia, dyspnea and paresthesia were reported in two patients each (2.4% each). The rate of these events in patients receiving conventional plasma was not significantly different.

b. Adverse Events in Subpopulations

1. Healthy Subjects

In the two randomized studies in healthy subjects, the only AE that occurred in ≥5% of subjects was headache, reported by 14% of subjects in the test group and 17% in the control group.

2. Congenital Coagulation Factor Deficiency

In the open label study of patients with congenital coagulation factor deficiencies, the most frequently reported AEs included: headache (50%), urticaria (38%), nausea (24%) and rigors (21%), which likely represent acute allergic transfusion reactions (discussed below). Subjects in this study were exposed to allogeneic plasma prior to enrollment and the observed AEs were expected with plasma transfusion.

3. Acquired Coagulopathy

In the prospective studies of patients with acquired coagulopathy as a result of liver disease, the high rate of patients reporting AEs (95%) reflects the high rate expected in this very ill population, including many undergoing liver transplantation. More than 20% of subjects in each cohort experienced nausea and post-procedural pain. Other frequent AEs (>10% in either arm) are largely reflective of the underlying disease and the procedures performed, and included tachycardia, ascites, constipation, diarrhea, vomiting, catheter site hemorrhage, edema, liver function abnormalities (ALT increased, AST increased), blood creatinine increased, abnormal liver function test (not specified), urine output decreased, electrolyte imbalance, hyperglycemia, hypokalemia, hypomagnesemia, metabolic acidosis, agitation, insomnia, dyspnea, pleural effusion, and hypertension and hypotension.

In the retrospective study in patients undergoing liver transplant, the only adverse events that were collected were HAT and mortality.

4. Thrombotic Thrombocytopenic Purpura and Discussion of Cardiac Disorders

In the TTP study, 100 percent of patients in the test group and 88.9% of patients in the control group experienced AEs. The most frequently reported AEs were

hypokalemia, insomnia, TTP (refractory or relapsed), constipation, urticaria, nausea, and pruritus. AEs were reported in 7 of 8 patients in Cycle 2.

Transfusion reactions were reported in 1 test and 1 control patient. Patient -(b)(6)- (test) had a delayed transfusion reaction secondary to Duffy A antibody. Patient -(b)(6)- (control) had a transfusion reaction of "itching, hives and facial swelling" reported on Day 3, moderate in severity, which resulted in study discontinuation. The patient received non-study TPE without further reported reactions. The low incidence of transfusion reactions may be due to the use of steroids in all patients and the frequent use of prophylactic antihistamines (17/17 test and 15/18 control). One control patient (-(b)(6)-) had TRALI reported on Day 1. The event was reported as serious and severe in intensity. This patient continued in the trial and received a total of 14 study TPEs without further incident. Two patients died during participation in the trial: 1 test patient with refractory TTP and 1 control patient with respiratory failure.

No antibodies to potential amotosalen neoantigens were detected during the trial.

AEs mapped to the Cardiac Disorders SOC were more common in the test group (29.4%, 5 patients) than in the control group (0.0%). Preferred terms mapped to this SOC in the test group included 3 patients with angina (one also with bradycardia and another one also with sinus arrhythmia), and 1 patient each with cardiac arrest and tachycardia. There were no patients with any AEs mapped to the Cardiac Disorders SOC in Cycle 2. Cerus further reviewed the database and added an additional 5 reports of "chest pain/tightness/discomfort" in 4 additional patients (2 in each treatment group) to those with potential cardiac AEs. Each of the additional patients were coded to a preferred term of chest pain or chest discomfort and mapped to the primary SOC axis of General Disorders and Administration Site Conditions.

Cerus arranged for an independent review of the case report forms by an expert in cardiac disease to further investigate the discrepancies they found between some of the reported AE verbatim terms and the original patient medical records. The cardiology expert concluded: "When medical records were reviewed blinded to treatment assignment, cardiac adverse events were rarely observed during treatment with study plasma. The single cardiac event (transient QT prolongation) observed in this study after initiation of TPE was determined to be due to a metabolic abnormality and was unrelated to such treatment. Episodes of chest pain were observed during treatment in a number of patients, none of which were found to be of definite cardiac origin, and none of which could be attributed to treatment with study plasma." The cardiology expert attributed the QT prolongation to hypokalemia.

A summary of cardiac AEs reported by the study sites and the cardiology expert conclusions is shown in table below.

Cardiac Adverse Events[a]: Study Site vs. Cardiology Expert CRFs

Patient ID	Treatment Group	Cardiac AE Per Study Site CRF (Verbatim Terms)[b]	Cardiac AE Per Cardiology Expert CRF	Cardiology Expert Comments
-(b)(6)-	Test	Chest pain secondary to respiratory distress	No	Chest pain during TPE attributed to pulmonary edema due to acute volume overload
-(b)(6)-	Test	Cardiac arrest	No	Anaphylaxis to FFP
		Chest tightness-intermittent	No	Non-cardiac chest pain during TPE
-(b)(6)-	Test	Chest discomfort, pain (cardiac)	No	Non-cardiac chest pain during TPE
		Bradycardia , intermittent	No	Not identified as an AE
-(b)(6)-	Control	Presumed non-cardiac chest pain	No	No chest pain identified
-(b)(6)-	Test	Chest tightness	No	Non-cardiac chest pain during TPE
-(b)(6)-	Control	Chest discomfort	No	No chest pain identified
-(b)(6)-	Test	Chest pain (cardiac)	No	Non-cardiac chest pain during non-trial TPE
-(b)(6)-	Test	Sinus arrhythmia	Yes	QT interval prolongation on EKG
		Midsternum pain (cardiac)	No	Non-cardiac chest pain during TPE
-(b)(6)-	Test	Intermittent tachycardia	No	Not identified as an AE

[a]Includes AEs mapped to Cardiac Disorders SOC and AEs of chest pain/discomfort/tightness.
[b]Terms in parentheses are query responses.

FDA's cardiology experts judged that most of the AEs were non-cardiac in origin. They stated that two of the SAEs could be cardiac in origin but that non-cardiac explanations were also plausible. The table below shows the results of the assessment by the FDA expert.

Results of the Assessment from FDA

Patient ID	Age-Sex	Treatment Group	AE	Evaluation of Cardiology Expert Requested by Cerus	FDA expert reviewers
(b)(6)	60F	Test	Chest pain, respiratory distress	Non-cardiac	Non-cardiac
(b)(6)	56F	Test	Cardiac arrest	Non-cardiac	Possibly cardiac
(b)(6)	65F	Test	Chest pain	Non-cardiac	Possibly cardiac
(b)(6)	34F	Control	Chest pain	Non-cardiac	Non-cardiac
(b)(6)	48F	Test	Chest tightness	Non-cardiac	Non-cardiac
(b)(6)	35F	Control	Chest discomfort	Non-cardiac	Non-cardiac
(b)(6)	47F	Test	Chest pain	Non-cardiac	Non-cardiac
(b)(6)	28F	Test	Chest pain, QT_c prolonged	Non-cardiac	Non-cardiac
(b)(6)	20M	Test	Tachycardia	Non-cardiac	Non-cardiac

For the two events assessed as possibly cardiac, the FDA experts concluded that Patient -(b)(6)- may have experienced a cardiac arrest due to a transfusion reaction, considered to be an anaphylactic reaction, but a, "cardiac arrhythmia e.g., ventricular tachycardia, may also have caused this event. The rhythm during the cardiac arrest is not recorded. The episodes of chest pain and chest tightness were not typical of ischemia." Also, "Patient -(b)(6)- may have had chest pain due to ischemia given her strong history for atherosclerotic vascular disease (stroke and possibly myocardial infarction). The negative biomarkers (cardiac enzymes were not elevated), nonspecific T wave abnormalities on EKG, and non-diagnostic dipyridamole stress test do not rule out an ischemic etiology with certainty."

The FDA expert concluded overall that there was no clear pattern of a cardiac origin for the AEs reviewed. However, the relationship between the IBS processed plasma and the cardiac adverse events cannot be ruled out and remains a potential safety concern in patients receiving very large volumes of IBS processed plasma.

5. Serious Adverse Events

a. Randomized Controlled Trials

In the combined RCT analysis, a large proportion of subjects had serious adverse events (SAEs) (test 60%, control 63%; p=0.754), reflecting the highly morbidity due

to the underlying diseases and treatments in patients with acquired coagulopathies, many of whom underwent liver transplantation, and in patients with TTP requiring TPE treatment. No statistically significant differences between treatment groups were observed for any preferred term or SOC.

b. Serious Adverse Events in Subpopulations

1. Healthy Subjects

There were no serious adverse events reported in the two prospective studies in healthy subjects.

2. Congenital Coagulation Factor Deficiency

Only one SAE was reported in this trial, an event of "airway obstruction" coded to the preferred term of obstructive airways disorder, severe in intensity and reported as possibly related to study FFP. This event occurred during endotracheal intubation for an elective cerebral angiogram with therapeutic embolization. The difficulty in intubation of this subject was attributed to laryngospasm, which occurred 3 hours after receiving IBS processed plasma and was reviewed by the DSMB for the study. The DSMB assessed the SAE as being unrelated to IBS processed plasma administration. The patient received further IBS processed plasma to treat his coagulopathy (Factor IX deficiency) following the procedure and recovered without clinical sequelae.

3. Acquired Coagulopathy

A large proportion of subjects in this subpopulation reported SAEs. In the single dose study (C-002-98), 10 SAEs were reported to occur in 5 patients (2 test, 3 control). One event was reported twice (as pulmonary edema and fluid overload) and was only included once in the analyses. All SAEs were considered to be unrelated to study transfusion except those for a single test patient. This patient received 1589 mL of IBS processed plasma over an 8 hour period and then developed signs of fluid overload with tachycardia, which were ascribed to the transfusion. The transfusion was stopped and the patient recovered without sequelae after treatment with diuretics.

In the larger prospective study of subjects with acquired coagulation deficiencies, 63% of test patients and 66% of control patients experienced an SAE (p=0.851). The highest frequency of SAEs was in the gastrointestinal system in both groups, with ascites as the single most frequent SAE (6.7% Test, 9.8% Control). Of note, there were no differences observed in the frequency of hepatic artery thrombosis, other thromboembolic events, and accelerated fibrinolysis between the test and control groups. There were a total of 6 severe adverse events, 3 in the test group and 3 in the control group, that were assessed by the Investigators as being "possibly related" to study FFP transfusion. These events included HAT post-OLT in two control patients and one test patient, fluid overload in one control patient, hematemesis in one test patient and hemoptysis in one test patient. There were no notable differences between groups for these events. All events were reviewed by the DSMB and adjudicated as being not related to study transfusion**.**

There were no statistically significant differences for any SAE or organ system for either the liver transplant or non-transplant subgroups when analyzed separately with a single exception. In the non-transplant subgroup, there was a higher number of SAEs in the General Disorders category in the test group (n=6, 16%) than in the control group (n=0). However the individual events were diverse with no common mechanism and included hemorrhage (n=1), mental status changes (n=1), multi-organ failure (n=3) and pyrexia (n=1). Thus the differences between treatment groups noted for this category is considered not clinically meaningful due to lack of a consistent mechanism or relationship. For the transplant subgroup, the trend was in the opposite direction, with no General Disorders events in the test group and 4 (14%) in the control group, including drug intolerance (n=1), edema lower limb (n=1) and pyrexia (n=2). The lower frequency of SAEs in the test group in a subset with higher exposure to IBS processed plasma is supportive of the conclusion that IBS processed plasma does not induce increased treatment related morbidity.

In the retrospective study of subjects with acquired coagulopathies undergoing liver transplantation, the key safety data that were reviewed included only HAT and mortality. In this study, there were also no significant differences between the test and control cohorts for either HAT (2.3% test vs. 5.1% control, p=0.242) or mortality (4.7% test vs. 3.8% control, p=0.789).

6. Long-term Safety

Six clinical trials included 42 healthy subjects and 108 patients who received IBS processed plasma. Many of these patients had repeated exposure to IBS processed plasma over variable periods of time, and for 17 patients undergoing TPE, the exposure to IBS processed plasma was large. No unexpected adverse events were identified as related to transfusion of IBS processed plasma in clinical trials, however, since some cardiac AEs in TTP treated patients remain a potential safety concern, this is reflected in the Warnings and Precautions and clinical studies sections of the device labeling.

Subjects who received IBS processed plasma over the longest duration of time were patients with congenital coagulation factor deficiencies (F3A99UC) who could continue treatment with IBS processed plasma for as long as the trial was open (approximately 18 months). The mean duration of treatment in this group was 45.6 days, with a maximum duration of 428 days (date of last study transfusion – date of first study transfusion +1). However, many subjects in this study received only a single transfusion for the purpose of PK analysis. Subjects in the TTP studies also received treatment over a fairly long duration of time, especially in the retrospective study. In the prospective TTP study, Cycle 1 exposure was limited to 35 days, and subjects who did not achieve remission within 30 days, or who relapsed within 65 days of initial remission were treated in a second cycle. In the retrospective TTP study, the first two documented cycles of TPE were included with no restriction on duration of TPE treatment or on the interval between these cycles. However in both studies, the majority of patients only received a single cycle of TPE. In the studies of TTP, the mean duration of treatment in the IBS group (test) was 42.5 days with a maximum of 802 days. Importantly, data were limited to two cycles of daily TPE, and thus

where treatment was over a long duration, it was indicative of a long interval between the two cycles, during which no study plasma transfusion was administered.

Peak post transfusion plasma levels of amotosalen in healthy subjects and patients occurred immediately after transfusion, and residual amotosalen levels declined rapidly. Amotosalen did not accumulate in recipient's plasma with repeated exposure in patients with either hepatic or renal dysfunction. Of specific importance, no patients developed immune responses to IBS processed plasma or evidence of circulating anticoagulant inhibitors after repeated exposure to IBS processed plasma

7. World-wide Marketing Experience; Postmarketing Safety Data

In addition to the prospective and retrospective clinical studies described in the preceding sections, two large sets of data have been obtained from prospective hemovigilance programs, including one overseen by Cerus (CLI-HV 00043) and one overseen by the French regulatory authority (ANSM) summarized in the table below.

Postmarketing Hemovigilance Programs for IBS Processed Plasma

Study	Design	Population	N
Cerus CLI-HV 00043	Prospective, Open Label, Non-Controlled Active Hemovigilance	All Recipients	9,667 patients 57,171 IBS processed plasma components 22,101 transfusion episodes
ANSM HV	Prospective, Open Label, Controlled Active Hemovigilance	All Recipients	144,065 IBS processed plasma components

a. Hemovigilance Study CLI-HV 00043

The Cerus-sponsored active hemovigilance program included data for 57,171 IBS processed plasma components transfused to 9,667 patients in 22,101 transfusion episodes at five centers in Spain, France and Belgium. There was no patient selection, randomization, or a requirement to recruit based on inclusion or exclusion criteria for this study. The primary outcome measure was the proportion of IBS processed plasma transfusions associated with acute transfusion reactions (ATR) and the proportion of patients experiencing an ATR. Event rates were expressed per transfusion episode and per patient because multiple plasma components were frequently transfused sequentially over a short period of time to each patient. Adverse events occurring within 24 hours after plasma transfusion were assessed by primary care physicians for relation to plasma transfusion. SAEs occurring within 7 days of plasma transfusion were reported and assessed by primary care physicians for relation to plasma transfusion. All AEs and SAEs classified as

possibly, probably, or definitely related to transfusion were classified as an ATR or serious adverse reactions (SAR) depending on the level of severity.

The population included in this study encompassed infants, children and adults with a broad range of indications, including congenital coagulation factor deficiency, acquired coagulopathy, immune deficiency, TTP, surgery and other non-specified medical indications. The mean age of study patients was 58.8 years (range <1 to 98 years). Most patients were adults, and they received the majority of IBS processed plasma (53,992 units), 440 infants received 1,125 IBS processed plasma components; and 355 children received 2,054 IBS process plasma components.

Subjects experienced an average of 2.3 transfusion episodes, with a very wide range of both number of transfusion episodes and total number of plasma components transfused. Although most patients (90.3%) in this cohort received more than one IBS processed plasma component, with 48 patients exposed to more than 60 plasma components, the majority of patients (59.8%) had only one plasma transfusion episode. Thirty seven percent of patients had between 2 and 10 plasma transfusion episodes and 2.3% of the patients had ≥11 plasma transfusion episodes.

Adverse events were reported following 53 of the 22,101 transfusion episodes (0.2%). ATR were reported following 41 transfusion episodes (0.2%). Serious adverse events were reported following 16 transfusion episodes (0.1%) and serious adverse reactions (SAR) were reported follow six transfusion episodes. Adverse events and ATR were expressed per transfusion episode and per patient and are summarized in the table below.

Frequency of Adverse Events, Serious Adverse Events, Acute Transfusion Reactions, and Serious Adverse Reactions[2] (CLI 00043)

	Rate Per Transfusion Episode (n = 22,101)		Rate Per Patient (n = 9,667)	
Outcome	**N**	**Rate per 10^3**	**N**	**Rate per 10^3**
All AEs	53	2.4	44	4.6
Severe AEs	17	0.8	17	1.8
ATR	41	1.9	32	3.3
SAE	16	0.7	16	1.7
SAR	6	0.3	6	0.6
Death	1	.0010	11	1.1

2 The following are standard FDA definitions for the following:

- Adverse Event (AE) – any undesirable experience associated with the use of a product in a subject
- Serious Adverse Event (SAE) – any adverse event that leads to death, is life threatening, leads to hospitalization, disability or permanent damage, birth defect, or other important medical events requiring medical or surgical treatment.
- Acute Transfusion Reaction (ATR) – a response or effect temporally related to administration of blood or blood components
- Serious Adverse Reaction (SAR) – a serious adverse event that has a reasonable possibility to have been caused by the product.

Overall, there was no transfusion-related sepsis reported and no cases of TRALI were considered to be related to the transfusion of IBS processed plasma. The incidence of AEs and ATRs was low, which may be due to the limitation of any post market surveillance study. The most frequently reported signs and symptoms of the ATRs were also consistent with recognized signs and symptoms associated with conventional plasma transfusions, and consistent with those noted in previous IBS processed plasma studies.

Eleven deaths were reported in this group of patients (n=9,667). The deaths were attributed to progression or complications of the patient's underlying disease and were considered unrelated to the transfusion of IBS processed plasma. However, one patient with hepatic cirrhosis, hemorrhagic shock and prior cardiac insufficiency experienced volume overload following transfusion that may have contributed to his death associated with pulmonary edema, respiratory distress and cardiac failure/arrest.

b. Hemovigilance Program ANSM HV

Since 2009, IBS processed plasma has been monitored in France through a hemovigilance program. It has been monitored as a unique plasma component and in comparison to other types of plasma treated with pathogen inactivation approved in France, i.e., solvent detergent and methylene blue,. (Andreu, Morel et al. 2002). Data were extracted from the published annual reports for hemovigilance (Rapport Annuel Hémovigilance) for 2009, 2010, and 2011. In this program, data are reported on a per component basis. Safety data for transfusion of a total of 144,065 IBS processed plasma components were monitored in this program, which provides an independent assessment of safety for IBS processed plasma. The data for plasma components other than IBS processed plasma provides concurrent control data and context for observed transfusion reaction rates.

During the 3 year period after implementation of IBS processed plasma in routine use, the rates of ATR for IBS processed plasma have been comparable to those of other plasma components, approximately 0.4 events per 1,000 plasma components. No hemorrhagic adverse events attributed to inadequate therapeutic responses were reported. The vast majority of ATRs were of low to moderate intensity and of the type expected with transfusion with conventional plasma. A single case of TRALI was reported in association with IBS processed plasma; however this may be underreported since this is a passive safety reporting system. The overall reduction in ATR rates from 2009 to 2011 may have been due in part to the widespread preference for use of male plasma.

8. Overall Safety Conclusions

Collectively the safety data support the conclusion that IBS processed plasma is safe and well tolerated for the intended use.

X. FINANCIAL DISCLOSURE

None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 21 CFR 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Hematology and Pathology Devices Panel or an FDA advisory committee for review and recommendation because no new scientific questions have arisen.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The INTERCEPT Blood System for Plasma reduces blood borne pathogens, including viruses, bacteria, and protozoan parasites, as well as donor leukocytes, without significantly affecting the function of plasma proteins.

The results of non-clinical studies of the IBS for Plasma have demonstrated:

- *In vitro* reduction of many major transfusion-transmitted pathogenic organisms found in plasma components, including cell-free and cell-associated viruses enveloped viruses, single-stranded and double-stranded DNA and RNA viruses, gram-positive and gram-negative bacteria, aerobic and anaerobic bacteria, and protozoan parasites; non-enveloped viruses and bacterial spores were resistant to IBS treatment

- Reduction in the risk of infection of patients due to organisms in plasma transfusions is expected

- Maintenance of adequate *in vitro* plasma protein function

- Lack of organ toxicity of amotosalen and of its photoproducts at the documented exposure levels (although cardiac toxicity could not be entirely excluded) and the absence of any indication in vivo of the risk of immunogenicity, genotoxicity, carcinogenicity, local toxicity or phototoxicity

- Reduction in the activity of T-cells, thereby lowering the risk of transfusion-associated graft-versus-host disease.

The results of clinical studies investigating the safety and effectiveness of IBS processed plasma have demonstrated:

- IBS processed plasma is safe and effective when used as coagulation factor replacement therapy in patients with multiple, acquired coagulation factor deficiencies, and when used for the exchange of plasma to treat TTP

- The acceptable overall safety profile of IBS processed plasma; adverse events reported in clinical trials were consistent with the types and frequency of adverse events expected in populations for which conventional FFP transfusion is indicated

- There was no accumulation of amotosalen with repeated large volume transfusions or with repeated long term exposure; no inhibitors or antibodies to potential amotosalen-induced plasma neoantigens were detected.

A. Benefit-Risk Conclusions

1. Estimating the Transfusion-Transmitted Infection (TTI) Exposure Risk

Residual risks for contamination in the blood supply have been characterized as "low" when considered on a per-donation basis.

Current Estimates of Per-Donation Exposure to Selected Infectious Agents

Infectious Agent	Per Donation Risk for TTI	Citation
HIV	1 in 1,467,000	(Zou et al. 2010)
HCV	1 in 1,149,000	(Zou et al. 2010)
HBV	1 in 280,000	(Zou et al. 2009)
WNV	1 in 350,000	(Petersen et al. 2005)
HTLV I/II	1 in 2,993,000	(Dodd et al. 2002)
Bacteria in apheresis platelet concentrates	1 in 1,500 -3,000	(Dumont et al. 2010)
CMV	1 in 435	(Wu et al. 2009)

Consideration of risk must also take into account the number of units transfused to a given patient. Patient exposure to plasma products is related to the underlying indication for transfusion; the higher the exposure, the greater the risk to any individual patient.

For example, treatment of TTP may expose the patient to up to 200 donors due to repeated therapeutic plasma exchange. Blood donors are tested by nucleic acid assays for infection with a limited group of viral pathogens which may be transmitted by FFP including HIV, human T-lymphotropic virus (HTLV), hepatitis b virus (HBV), hepatitis c virus (HCV), and West Nile Virus (WNV). For example, the risk of exposure to HBV with transfusion of plasma from 200 different donors is estimated to be approximately 1 in 1,750 (Zou et al. 2009).

Bacterial contamination of FFP is rare due to frozen storage, but is still reported. Five cases of bacterial contamination of FFP were reported in Canada from 2002-2003 and five cases in Germany from 1997-2007. Organisms identified included species of *Staphyloccoccus, Klebsiella, Propionibacterium* and *Pseudomonas,* although waterbaths used to thaw the plasma (rather than donors) were identified as the potential source of *Pseudomonas* contamination in some instances (Pandey 2012).

Likewise, although transmission of leukotropic viruses (CMV, HTLV) is not typically associated with plasma transfusion since FFP is considered non-cellular, several studies have shown significant numbers of WBCs contaminating plasma units pre-freeze (Pandey 2012). A major risk of infection to patients treated with repeated exposure to plasma

transfusions is from emerging pathogens or from recognized pathogens for which testing is not currently in place, for example dengue virus (Mohammed et al. 2008).

The use of pathogen reduced plasma is reasonable on the basis of the risk of TTI versus the benefit of preventing TTI for existing or potential emerging pathogens.

2. Estimation of Excess Treatment Related Morbidity of the Pathogen Inactivation Intervention

The estimation of excess risk of treatment related morbidity can be derived from the clinical trial experience and the post-marketing surveillance experience. These studies have not identified any adverse events specifically attributable to the IBS processed plasma. The most common adverse reactions in the RCTs (reported as possibly or probably related to IBS processed plasma and occurring in 2 or more study subjects) were of minor severity and included: pruritus (7.2%), urticaria (6%), hypokalemia (4.8%), anemia (3.6%) and nausea (3.6%). Vomiting, pyrexia, rigors, hypomagnesemia, dyspnea and paresthesia were reported in 2 patients each (2.4% each). The rate of these events in patients receiving conventional plasma was not significantly different than the rate in patients receiving IBS processed plasma. There does not appear to be any excess treatment-related morbidity associated with IBS processed plasma compared to the use of conventional plasma lacking the benefit of pathogen inactivation.

a. Risk of Transfusion Reaction

Transfusion reactions and/or symptoms of transfusion reactions were reported more frequently in subjects with congenital coagulation factor deficiencies, which is not surprising given the higher prior exposure to blood products. In prospective controlled trials, transfusion reactions were comparable between patients who received IBS processed plasma and those who received conventional plasma.

In the post-marketing hemovigilance program conducted by Cerus (9,667 patients), only 0.3% of patients experienced an acute transfusion reaction (ATR); and 0.2% of the transfusion episodes were associated with an ATR. The most frequently reported ATRs were consistent with those of conventional plasma transfusions, and consistent with those noted in prospective and retrospective IBS processed plasma studies. However typical passive postmarketing reporting usually results in an underreporting of these types of events; therefore the rates of these reactions cannot be compared to that of conventional plasma.

Following commercialization in Europe, serum and/or plasma samples from seven patients with suspected allergic transfusion reactions after receipt of IBS processed plasma were tested for antibodies to amotosalen-associated proteins. To date, all samples tested have been negative for IgE, IgG and/or IgM antibodies against amotosalen in the treated plasma in an -(b)(4)- assay.

b. Risk of Transfusion Related Acute Lung Injury

Transfusion related acute lung injury (TRALI) is a leading cause of transfusion-related mortality. No cases of TRALI have been reported in any subjects who received IBS

processed plasma in the prospective or retrospective clinical studies. A single case was reported in study F3C99 in a control patient. The event was reported on day 1 as serious, severe in intensity, and "probably related" to study FFP. This patient continued in the study and received a total of 14 study TPEs without further incident.

A single case of TRALI was reported in association with IBS processed plasma in the independent French hemovigilance program of a total of 144,065 units of IBS processed plasma transfused over 3 years, although this is most likely underreported in such a passive reporting system. In the Cerus hemovigilance program, 4 of 9,667 patients (57,171 units of IBS processed plasma) had signs or symptoms compatible with acute lung injury. However, in each case, transfusion-related acute lung injury attributed to the transfusion of IBS processed plasma could not be confirmed based on co-morbidity or the transfusion of other blood products including RBC or platelets. Current therapy with FFP, using only male donors, carries a risk of TRALI of approximately 1:7,000 units to 1:20,000 units. (Toy, Gajic et al. 2012).

c. Risk of Bleeding

Overall, the incidence of hemorrhagic AEs was similar between treatment groups and the types and severity of hemorrhage were consistent with underlying disease processes. IBS processed plasma prevented and controlled bleeding in patients with liver disease, liver transplantation, and TTP with severe thrombocytopenia comparably to FFP.

d. Risk of Thromboembolism

Some types of plasma have been reported to have an increased risk of thrombotic events due to lower levels of antithrombotic proteins (Flamholz, Jeon et al. 2000), (Yarranton, Cohen et al. 2003). Six cases of HAT were reported in the prospective F3B99 trial (2 test and 4 control). HAT is a recognized complication of liver transplantation. During the post-marketing study of liver transplant (EFS-Alsace) the incidence of HAT was 5.1% in the control plasma group and 2.3% in the test group. These frequencies for HAT are within the expected range for liver transplantation (Nghiem et al. 1996).

e. Risk of Cardiac Events

Cardiac events such as angina and arrhythmias occurred in the setting of TTP in patients who received multiple IBS processed plasma units and consequently the highest cumulative dose of amotosalen. It is not certain whether these events are causally related to the product or due to the underlying disease. However, since this is a safety concern, it has been added to the Warnings and Precaution and Clinical Studies sections of labeling.

3. Benefit and Risk Summary Conclusion

Disorders such as liver disease, liver transplantation and TTP are highly morbid conditions that often require repeated exposure to plasma products. Because of the large volume plasma exposures required to support these patients, they are especially

vulnerable to contaminating or emerging pathogens in plasma. The clinical experience in TTP and liver disease and transplant support the effectiveness and safety of IBS processed plasma.

B. Overall Conclusions

On the basis of this cumulative experience, it is concluded that there is no excess treatment-related morbidity associated with IBS processed plasma compared to the use of conventional plasma. There are no unexpected adverse events and no events specifically related to IBS processed plasma. The benefit of pathogen inactivation provides a favorable benefit to risk profile for prevention of transfusion-transmitted infections.

XIII. CBER DECISION

CBER issued an approval order on December 16, 2014. The final conditions of approval cited in the approval order are described below.

The applicant's manufacturing facilities: ----------(b)(4)----------, have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.
Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

None

APPENDIX 1

Graded Scale for Hemostatic Assessment

MUCOCUTANEOUS	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Epistaxis	none	<1 hour in duration	>1 hour duration	*	**
Oropharyngeal	none	<1 hour in duration	>1 hour duration	*	**
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	petechiae of skin or mucosa, purpura <1 inch diameter, confluent purpura	purpura >1 inch in diameter, generalized petechiae or purpura of skin	*	**
GASTROINTESTINAL					
Melena	none	N/A	positive occult blood	*	**
Rectal bleeding/hematochezia (visible blood)	none	N/A	positive occult blood	*	**
Covert GI bleeding (no visible blood; not black or tarry stools)	none	positive occult blood	see melena/ hematochezia	*	**
Hematemesis	none	N/A	Positive visual/ occult blood	*	**
GENITOURINARY					
Hematuria	none	up to 1+ (slt, trace, small)	2+ (moderate) or greater	*	**
Vaginal bleeding, abnormal	none	spotting, <2 saturated pads/day	>2 saturated pads / day	*	**
BRONCHO-PULMONARY					
Hemoptysis	none	N/A	positive	*	**
MUSCULOSKELETAL & SOFT TISSUE	none	N/A	spontaneous hematoma; joint bleeding	*	Permanent debilitating change; **
BODY CAVITY					
Pleural, peritoneal, pericardial, retroperitoneal	none	N/A	red cells on microscopic exam	grossly bloody	**
CENTRAL NERVOUS SYSTEM					
CNS bleeding/ hemorrhage	none	N/A	N/A	bleeding on CT w/o clinical consequences	non fatal bleeding with neurological signs & symptoms
Retinal bleeding	none	retinal bleeding w/o visual impairment	N/A	N/A	visual impairment, i.e. field deficit
INVASIVE SITES					
All	none	N/A	any bleeding around catheter; bleeding at venipuncture sites	*	**

* Requiring red cell transfusion specifically for support of bleeding within 24 hours of onset. If bleeding is continuous and the onset grading was grade 1 or 2 at onset, increase the severity grade when red cell support is needed.
** Bleeding associated with hemodynamic instability and/or fatal bleeding.
N/A: For categories with N/A under the grade means that the score is not used for that system. You must choose from the remaining scores.

Source: Table 16.1.11, Transfusion of S-59 Fresh Frozen Plasma in Patients with Congenital Coagulation Factor Deficiencies; Final Report, Version 2.0