A PHASE 1, SINGLE-CENTER, PARTIAL DOUBLEBLIND, RANDOMIZED, CONTROLLED (VERSUS FRESH FROZEN PLASMA [FFP] IN COHORT 3 ONLY) CLINICAL STUDY OF THE SAFETY OF ASCENDING DOSES OF AUTOLOGOUS FREEZE DRIED PLASMA (FDP) IN HEALTHY VOLUNTEERS

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Sponsor
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INVESTIGATOR'S AGREEMENT

A PHASE 1, SINGLE-CENTER, PARTIAL DOUBLE-BLIND, RANDOMIZED, CONTROLLED (VERSUS FRESH FROZEN PLASMA [FFP] IN COHORT 3 ONLY) CLINICAL STUDY OF THE SAFETY OF ASCENDING DOSES OF AUTOLOGOUS FREEZE DRIED PLASMA (FDP) IN HEALTHY VOLUNTEERS

"I have read this protocol and agree to conduct the study as outlined herein in accordance with International Conference on Harmonisation Good Clinical Practice Guidelines and Food and Drug Administration (FDA), Department of Defense, and United States Army Regulations."

_____ _____

Jose A. Cancelas, MD, PhD
Principal Investigator
Hoxworth Blood Center/University of Cincinnati

Date

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2. SYNOPSIS

Name of Sponsor:
The Surgeon General, Department of the Army

Name of Investigational Product:
RePlas™

Name of Active Ingredient:
Human Plasma, Freeze Dried

Title of Study:
A Phase 1, Single-Center, Partial Double-Blind, Randomized, Controlled (versus Fresh Frozen Plasma [FFP] in Cohort 3 only) Clinical Study of the Safety of Ascending Doses of Autologous Freeze Dried Plasma (FDP) in Healthy Volunteers

Study Center(s):
Hoxworth Blood Center/University of Cincinnati

Principal Investigator:
Jose A. Cancelas, MD, PhD

Study Period (years):	**Phase of Development:** 1
Estimated date first subject enrolled: February 2017 Estimated date last subject completed: July 2018	

Objectives:

Primary: The primary objective of this study is to assess the safety of single infusions with the RePlas™ FDP product at increasing fixed doses of either 1 unit (approximately 270 mL), 2 units (approximately 540 mL), or 3 units (approximately 810 mL) in normal healthy subjects. In the 2 lower dose cohorts, safety will also be assessed in terms of the type of autologous plasma used as the starting material in the manufacture of the investigational product:

- RePlas™ FDP product manufactured from autologous FFP derived from whole blood (WB) donations where Citrate Phosphate Dextrose (CPD) is the anticoagulant, or RePlas™ FDP-CPD; and
- RePlas™ FDP product manufactured from autologous FFP collected during plasmapheresis where Acid Citrate Dextrose (ACD) is the anticoagulant, or RePlas™ FDP-ACD.

The highest dose cohort will receive FDP manufactured only from FFP collected by plasmapheresis (FDP-ACD). Conclusions on whether the study meets its safety objectives will be based only on treatment emergent adverse events (TEAEs). TEAEs are adverse events (AEs) that occur after administration of the study treatment, plasma infusion, has begun. AEs occurring prior to treatment (e.g., AEs that occur during autologous plasma collection) will not be considered relevant to the study's objectives.

Secondary: The secondary objectives are to:

- Assess the safety of a fixed-dose infusion of 3 FDP units (approximately 810 mL) in comparison to infusion with the same dose of autologous FFP collected during plasmapheresis; and
- Determine if the changes in specific coagulation factors, hematology, and chemistry values are similar within clinically meaningful levels after infusion of either 3 units of autologous FDP or FFP.

Methodology:

Overview. This single-site, partial double-blind study in healthy volunteers is designed to assess the safety of infusing ascending doses of reconstituted autologous FDP in 3 fixed-dose cohorts. Subjects in Cohort 1 will receive 1 unit of FDP, which is approximately 270 mL. Subjects in Cohort 2 will receive 2 units of FDP, which is approximately 540 mL. Subjects will be enrolled for a specific dose cohort beginning with the lowest dose in Cohort 1. In the absence of TEAEs or implementation of protocol stopping rules (SR), subjects will be enrolled in Cohort 2. In both Cohorts 1 and 2, subjects will be methodically assigned to 1 of 2 single infusion treatment arms where they will receive the corresponding dose of either FDP-CPD or FDP-ACD, products manufactured with autologous plasma derived from WB or autologous plasma collected by plasmapheresis.

In the absence of TEAEs or implementation of protocol stopping rules (SR) in Cohort 2 subjects, infusions in Cohort 3 subjects may proceed. These subjects will receive 3 autologous FDP-ACD units (approximately 810 mL), which is the highest trial dose of the experimental product and undergo an additional separate infusion where they will receive the same dose of autologous FFP. Subjects participating in this randomized, controlled, crossover infusion treatment cohort will be randomized to a specific infusion schedule where they will first be infused with either 3 units of FDP or 3 units of FFP at the first infusion visit, followed by infusion with the alternate product at the second infusion visit. Crossover treatment of FDP and FFP enables comparison of infusion safety parameters and select coagulation factor recoveries between FDP and FFP within the same subject at this higher dose. Unlike Cohorts 1 and 2, the FDP and FFP infusion products in Cohort 3 will be sourced only from autologous plasmapheresis donations. A 2-week period between infusion visits is required for all Cohort 3 subjects regardless of the infusion schedule.

Collection of Autologous Plasma. Use of autologous plasma in the trial assists in the elimination of potential AEs related to allogeneic plasma infusion, but it also adds additional burden to participating subjects who, upon consent and enrollment, need to donate sufficient volume of plasma to provide the autologous plasma needed for the trial infusions (eg, manufacture of autologous FDP units in all cohorts; in Cohort 3, the additional need for FFP in addition to FDP). Blood donation standards typically require a 56-day interval between WB donations; however, an abbreviated donation period of 28 days will be in use for the duration of this study. Without the loss of red blood cells (RBCs) in plasmapheresis, these types of donations can be made more frequently, with an approximate 7 to 10 day interval between donations. Also, depending on the donor's size, plasmapheresis donations yield greater plasma volume per collection. Summarily, compared to WB collection, the use of plasmapheresis to net the per subject plasma volume required presents practical advantages to subjects (eg, requires fewer collection visits) while minimizing increased risk for Cohort 3 subjects. FDA's volume limits for automated collection of plasma are summarized and presented in the Collection Volume Limits via Plasmapheresis Collection table below (FDA-1992).

Collection Volume Limits via Plasmapheresis Collection

Donor Weight	Plasma Volume or Weight	Collection Volume*
10 – 149 lbs	625 mL (640 g)	690 mL (705 g)
150-174 lbs	750 mL (770 g)	825 mL (845 g)
≥175 lbs	800 mL (820 g)	880 mL (900 g)

*includes anticoagulant volume

As shown in the Cohort and Treatment Arm Details table below, subjects' assigned cohorts and treatment arms indicate the type, frequency, and total volume of blood/plasma donations required. Subjects in Cohorts 1 and 2 are to provide sufficient plasma volume for a single infusion with either 1 or 2 units, respectively, and based on assigned treatment arm, they are to provide plasma through WB

or plasmapheresis collection for manufacture of autologous FDP-CPD or FDP-ACD. Cohort 2 subjects in the FDP-CPD treatment arm are required to successfully make 2 WB donations within a relatively short period of time to provide adequate volume for their use in the trial. Because of the extraordinarily long time required to accrue sufficient WB-derived plasma for the high dose cohort (approximately 11 months), the FDP-CPD treatment arm is not included in Cohort 3. The total starting volume of plasma needed from each Cohort 3 subject is approximately 1,620 mL; triple that of Cohort 2 and thus inclusion of this treatment arm in Cohort 3 would require 6 WB donations, increasing subject risk for significant iron store depletion and anemia.

Cohort and Treatment Arm Details

Dose Cohorts and Treatment Arms	Number of Subjects	Donation Type	Approximate Volume Autologous Plasma Required	Number of Donations
Cohort 1: One unit single infusion [approximately 270 mL]				
Arm 1: FDP-CPD	4	WB	270	1
Arm 2: FDP-ACD	4	Plasmapheresis	270	1
Cohort 2: Two units single infusion [approximately 540 mL]				
Arm 3: FDP-CPD	4	WB	540	2
Arm 4: FDP-ACD	4	Plasmapheresis	540	1
Cohort 3: Three units crossover infusion [approximately 810 mL, each]				
Arm 5: FDP-ACD x FFP	4	Plasmapheresis	1,620	3-4[1]
Arm 6: FFP x FDP-ACD	4	Plasmapheresis	1,620	3-4[1]

[1] Assumes an average range of 600 to 800 mL donation volume.

Pharmacovigilance.

The study will be paused to assess the safety of study continuation using the following SRs that will be applied to all study subjects throughout the trial:

1. An SAE that is determined to be possibly, probably, or definitely related to the study product;
2. An AE related to the study product that the PI, RM, and/or the sponsor's PVG MD agree jeopardizes the subject's health or safety;
3. An AE related to the study product that requires medical or surgical intervention to prevent occurrence of an SAE;
4. A post-infusion, coagulation function assay result that is abnormal and also greater than a 20% change from the baseline value recorded for prothrombin time and international normalized ratio (PT/INR) and/or activated partial thromboplastin time (aPTT) (eg, a subject who has a baseline INR of 1.0 with a post-infusion INR of 1.3 will activate an SR, because this is an abnormal coagulation function assay result that is also a greater than 20% change from the pre-infusion assay result); and/or
5. Post-infusion development of deep vein thrombosis (DVT), cardiac ischemia, pulmonary embolism (PE), or hemolysis.

Data and Safety Monitoring Board (DSMB). A designated DSMB will formally review subjects' data following the completion of infusions in each cohort for the purpose of assessing safety. DSMB meetings will be scheduled to maximize the amount of subject data reported to the DSMB through the 28-day follow-up visit. The DSMB will have at a minimum all data through the 7-Day Follow Up Visit. Following each meeting, the DSMB will provide the sponsor with a recommendation about proceeding with infusions in the subsequent cohort. Following the meeting to review Cohort 3 data, the DSMB will provide a recommendation about proceeding with the next planned FDP trial. After the receipt and consideration of each DSMB recommendation, the sponsor will make a final determination about proceeding to the next cohort or the next FDP trial.

Estimated Number of Subjects to Screen: 48

Maximum Number of Subjects to Enroll: 24

Cohort 1, Arm 1: (n=4) subjects are to be infused with 1 autologous FDP unit (FDP-CPD) manufactured from WB-derived FFP.

Cohort 1, Arm 2: (n=4) subjects are to be infused with 1 autologous FDP unit (FDP-ACD) manufactured from FFP collected via plasmapheresis.

Cohort 2, Arm 3: (n=4) subjects are to be infused with 2 autologous FDP (FDP-CPD) units manufactured from WB-derived FFP.

Cohort 2, Arm 4: (n=4) subjects are to be infused with 2 autologous FDP units (FDP-ACD) manufactured from FFP collected via plasmapheresis.

Both arms of Cohort 3 are to be infused with 3 units of autologous plasma product at each of 2 infusion visits. Infusion visits are to be scheduled such that there is a period of no less than 2 weeks between infusions.

Cohort 3, Arm 5: (n=4) subjects will receive 3 autologous FDP units (FDP-ACD) manufactured from FFP collected via plasmapheresis at their first infusion visit followed by infusion with 3 autologous FFP units, collected via plasmapheresis, at their second visit.

Cohort 3, Arm 6: (n=4) subjects will be infused with these products in the opposite order as Arm 5 (eg, autologous FFP at first infusion and autologous FDP-ACD at the second).

Eligibility and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

1. Males and non-pregnant/non-breastfeeding females;
2. For females, a minimum weight of 140 pounds and a maximum weight of 220 pounds; for males a minimum weight of 140 pounds and a maximum weight of 250 pounds;
3. 18-55 years of age;
4. Self-reports that he or she feels well and healthy;
5. Scores ≥ 35 on the Duke Activity Status Index;
6. Able to donate a unit of WB or plasma by plasmapheresis based on the AABB donor history questionnaire with modifications indicated. Subjects with history of travel which puts them at risk for Creutzfeldt-Jakob Disease, malaria, or Zika will be eligible to participate;
7. Has read the educational materials on donating blood and has had his or her questions answered;
8. Able and willing to provide written informed consent;
9. Available and able to come to the treatment clinic for scheduled study visits for the duration of the trial, which is approximately 12 weeks for subjects in Cohort 1 and Cohort 2, Arm 4

and approximately 16 weeks for Cohort 2, Arm 3 and Cohort 3 (includes time for collections, product manufacture, and infusions);

10. Females of childbearing potential should either be surgically sterile (hysterectomy or tubal ligation), or should use a highly effective, medically accepted contraceptive regimen. Highly effective methods of birth control are defined as those which result in a lower failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, condoms with spermicide, or vasectomized partner;
11. All females must have a negative urine pregnancy test prior to enrollment; and
12. Understands the English language.

Exclusion Criteria:

1. Known liver, kidney, cardiovascular, neurologic, gastrointestinal, blood, endocrine/metabolic, autoimmune or pulmonary disease, or treated or untreated hypertension;
2. Cancer of any kind, under treatment or resolved;
3. Known or past coagulopathy conditions;
4. Any conditions, medications, etc. on the AABB medical deferral list;
5. Past history of asthma (defined as use of a prescribed daily asthma controller medication or required asthma medication in the past 2 weeks);
6. Past diagnosis of stroke, deep vein thrombosis, venous or arterial thrombosis, blood clots, or transient ischemic attack;
7. Family history of venous or arterial thrombosis before the age of 50 in first-degree relatives (i.e., biological parents, full siblings, or children);
8. D-dimer result ≥0.5 FEU/mL;
9. History of abnormal electrocardiogram (EKG);
10. Current smoker (defined as having smoked within the last 6 months);
11. Known Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS)-related illness or received a positive test result for HIV infection;
12. Positive test for Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) or Human T-cell Lymphotropic Virus (HTLV);
13. History or significant treated or untreated mental health issues;
14. Female subject who is pregnant, lactating, or with a positive pregnancy test;
15. Currently taking an antibiotic or another medication for an infection;
16. Treatment or use of aspirin (or other platelet inhibiting agents) within 14 days of study donation and infusion visits;
17. Currently using any medications for anticoagulant therapy;
18. Previous use of clotting factor concentrate(s);
19. Receipt of blood or blood products within the past 12 months;
20. In the past week, has had a headache and fever at the same time;
21. Known intolerance to any excipients (citrate) in the study drug formulation;
22. Systolic blood pressure greater than 140 mmHg;
23. Diastolic blood pressure greater than 90 mmHg;
24. Temperature greater than 100°F;
25. Known hematocrit less than 38% for both male and female donors;

26. Positive direct antiglobulin test (DAT);
27. Treatment with any investigational agent within 1 month before treatment infusion for this trial;
28. Participation in any phase of any other investigational trials while participating in this trial;
29. Unwilling or unable to comply with the requirements of this protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's return for follow-up visits on schedule;
30. Other unspecified reasons that, in the opinion of the PI, make the subject unsuitable for enrollment; or
31. Institutionalized because of legal or regulatory order.

Investigational Product Dosage, Schedule, and Mode of Administration:

Cohort 1, Arm 1: Subjects will be infused with 1 unit (approximately 270 mL) of autologous FDP-CPD.

Cohort 1, Arm 2: Subjects will be infused with 1 unit (approximately 270 mL) of autologous FDP-ACD.

Cohort 2, Arm 3: Subjects will be infused with 2 units (approximately 540 mL) of autologous FDP-CPD. **Cohort 2, Arm 4:** Subjects will be infused with 2 units (approximately 540 mL) of autologous FDP-ACD.

Cohort 3, Arms 5 & 6: Subjects will be infused with 3 units (approximately 810 mL) of autologous FDP-ACD and 3 units (approximately 810 mL) of autologous control FFP following a 2 week cross-over period. Subjects will receive in total 6 units (approximately 1,620 mL) over the course of 2 infusion visits. Subjects are to be randomized to treatment schedule arms that dictate the sequence for infusing FDP-ACD and FFP across the 2 infusion visits (eg, FDP-ACD at the first infusion followed by FFP or vice versa).

Duration of Treatment: *Cohort dependent*

Duration of Subject Participation, by Cohort and Treatment Arm Assignment

Cohort, Treatment Arm	Screening Period	WB/Plasma Collection Time	FDP Manufacturing Time	Planned Study Follow-up Period	Total Expected Duration
Cohort 1, Arm 1	~2 Weeks	1 Week	~5 Weeks	4 Weeks	~12 Weeks
Cohort 1, Arm 2	~2 Weeks	1 Week	~5 Weeks	4 Weeks	~12 Weeks
Cohort 2, Arm 3	~2 Weeks	~5 Weeks	~5 Weeks	4 Weeks	~16 Weeks
Cohort 2, Arm 4	~2 Weeks	1 Week	~5 Weeks	4 Weeks	~12 Weeks
Cohort 3, Arm 5	~2 Weeks	~3 Weeks	~5 Weeks	6 Weeks	~16 Weeks
Cohort 3, Arm 6	~2 Weeks	~3 Weeks	~5 Weeks	6 Weeks	~16 Weeks

The timeline for screening, autologous plasma collection(s), and FDP manufacturing are estimated. The time to complete WB/Plasma collection may be extended if needed to obtain the required amount of study plasma and will be assessed on a per-subject basis. The manufacturing time has been set at 5 weeks to allow time for shipping, manufacture, and testing of the FDP product.

The longest expected duration of subject participation is approximately 16 weeks for subjects in Cohort 2, Arm 3 and Cohort 3, Arms 5 and 6.

Reference Therapy, Dosage, Schedule, and Mode of Administration:

The reference therapy for this study is autologous FFP. Subjects in Cohort 3 are treated in a crossover design randomizing product infusion order across the two infusion visits. The initial infusion will be either 3 units of autologous FDP-ACD or 3 units of autologous control plasma (FFP). Subjects in Cohort 3 will receive a second infusion of reference product or investigational product, depending on their initial treatment. Subjects in Cohort 3 are to receive a total of 6 units of autologous plasma.

Criteria for Evaluation:

Primary Endpoints. The primary endpoints to be assessed are AEs, specifically TEAEs; SAEs; Suspected, Unexpected, Serious Adverse Reactions (SUSARs); and death.

Secondary Endpoints. In Cohort 3, the change in pre- and post-infusion measurement of the endpoints listed below will be compared:

- PT, INR, aPTT, Factors I, II, V, VII, VIII, IX, X, XI, D-Dimer, von Willebrand factor activity, Protein S activity, Protein C activity, PF 1+2, TAT, Antithrombin III, Alpha-2 Antiplasmin, and C3a des Arg compared to pre-infusion values after 3 unit infusion of FDP compared to 3 unit infusion of FFP; and
- Hematology, urinalysis, vital signs, DAT and chemistry values compared to pre-infusion values after 3 unit infusion of FDP compared to 3 unit infusion of FFP.

Statistical Methods:

Descriptive statistics will be used to present the study data. Categorical variables will be presented as number and percent of subjects for each outcome. For quantitative variables, summaries will include the sample size, mean, median, standard deviation, minimum, and maximum and 25^{th} and 75^{th} percentile. All data will be presented either as listings, summary tables, figures, or all 3. For summary descriptive statistics, missing data will be represented by counts; no adjustments will be made. For the crossover study (Cohort 3), descriptive statistics will be provided for each treatment, treatment by period (first or second administration), treatment by sequence (FDP then FFP [Sequence 1] or FFP then FDP [Sequence 2]) by period, and will include the sample size, mean, median, standard deviation, minimum, and maximum and 25^{th} and 75^{th} percentile.. All statistical analyses will be performed using SAS version 9.3 or higher (SAS Institute Inc., Cary, NC).

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Table 2: Abbreviations

Abbreviation	Explanation
ACD	Acid Citrate Dextrose
AE	Adverse Event, Adverse Experience
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
AST	Aspartate Aminotransferase
AT-III	Antithrombin III
BUN	Blood Urea Nitrogen
C3	Complement Factor 3
CAP	College of American Pathologists
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CO_2	Carbon Dioxide
CPD	Citrate Phosphate Dextrose
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAT	Direct Antiglobulin Test
DCR	Damage-Control Resuscitation
DIC	Disseminated Intravascular Coagulation
DIN	Donation Identification Number
DoD	Department of Defense
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eIT	Enterprise Information Technology
EKG	Electrocardiogram
FDA	Food and Drug Administration
FDP	Freeze Dried Plasma

Abbreviation	Explanation
FDP-ACD	Freeze Dried Plasma collected by plasmapheresis where Acid Citrate Dextrose was used as the anticoagulant
FDP-CPD	Freeze Dried Plasma derived from whole blood where Citrate Phosphate Dextrose was used as the anticoagulant
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
HBC	Hoxworth Blood Center
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HHS	US Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus (Types 1 and 2)
HRPO	Human Research Protections Office
HTLV	Human T-cell Lymphotropic Virus (Types 1 and 2)
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICSI	Institute for Clinical Systems Improvement
IgG	Immunoglobulin G
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
K	Potassium
Kg	Kilogram
LyP	Lyophilized Plasma
Mg	Milligram(s)
mL	Milliliter(s)
mmHg	Millimeter of Mercury
NBCUS	National Blood Collection and Utilization Survey Report
ORA	Office of Regulated Activities [formerly Division of Regulated Activities and Compliance (DRAC) and Clinical Services Support Division (CSSD)]
ORP	Office of Research Protections
PF 1+2	Prothrombin Fragment 1+2
PF24	Plasma frozen 24-hours after phlebotomy Plasma is refrigerated within 8 hours of phlebotomy.

Abbreviation	Explanation
PF24RT24	Plasma frozen 24- hours after phlebotomy Plasma is held at room temperature from the time of phlebotomy to freezer storage
pH	Logarithmic measure of hydrogen ion concentration
PI	Principal Investigator
PLTs	Platelets
pRBCs	Packed Red Blood Cells
PSSB	Product Safety Surveillance Branch, ORA, USAMMDA
PT	Prothrombin Time
PT/INR	Prothrombin Time and International Normalized Ratio
PVG MD	Pharmacovigilance Physician
RBC	Red Blood Cell
RM	Research Monitor
SAE	Serious Adverse Event
SOC	System, Organ, Class Designation
SOCOM	United States Special Operations Command
SOP	Standard Operating Procedure
SR	Stopping Rule
SUSAR	Suspected, Unexpected, Serious Adverse Reaction
SWFI	Sterile Water for Injection
TAT	Thrombin-Antithrombin Complex
TEAE	Treatment Emergent Adverse Event
TSG	The Surgeon General
TTP	Thrombocytopenic Purpura
UAE	Unexpected Adverse Event
ULN	Upper Limit of Normal
USAMMDA	United States Army Medical Materiel Development Activity
USAMRMC	United States Army Medical Research and Materiel Command
US	United States
USP	US Pharmacopeia
VSI	Vascular Solutions, Inc. (a wholly owned subsidiary of Teleflex)
vWF	von Willebrand Factor
WB	Whole Blood
WBC	White Blood Cell

5. INTRODUCTION

Recent studies have shown that early attention to coagulopathy in severely injured patients, and an earlier use of blood products (including plasma and platelets), may improve patient outcome (Borgman et al-2007, Holcomb et al-2007, Murad et al-2010).

FFP is plasma that is separated from a unit of whole blood (WB) and frozen within 8 hours of collection. FFP can also be manufactured from plasma collected during plasmapheresis; however, freezing must occur within 6 hours after collection. The anticoagulant used for collection of WB-derived FFP is Citrate Phosphate Dextrose (CPD), and for plasmapheresis-derived FFP, it is Acid Citrate Dextrose (ACD). Thawed plasma is FFP that has been thawed and stored at 4°C for as long as 5 days after thawing (AABB-2013). To treat hemorrhaging patients more quickly, many emergency rooms maintain thawed group AB plasma alongside "emergency release" group O packed red blood cells (pRBCs), which allows both the pRBCs and plasma to be used immediately (without the need to determine the blood type of the patient or crossmatch the red cells). The use of these "emergency release" blood products along with techniques such as implementation of a massive transfusion protocol, where blood products are transfused in a ratio of plasma:platelets:red cells of 1:1:1, result in reduced exsanguination rates in the first 24 hours and better hemostasis than a ratio of 1:1:2 in patients who are massively bleeding (Holcomb et al-2015, Novak et al-2015).

5.1. Limitations of Fresh Frozen Plasma Products

Currently, the only licensed plasma products with consistently high levels of clotting factors in the United States must be stored in the frozen state (FFP, plasma frozen 24 hours after collection and refrigerated within 8 hours (PF24), or plasma frozen 24 hours after collection and held at room temperature (20°C-24°C) until freezing (PF24RT24)). These plasma products can be made available in civilian trauma centers, emergency rooms, and surgery suites, but have several limitations that make it difficult for their use. First, they must be stored and transported frozen because they have a short shelf life once thawed. Second, it can take 20-40 minutes for frozen plasma to reach the hemorrhaging patient due to the preparation, thawing, and delivery time that is required. Although thawed plasma can be immediately available for use, it does not avoid the shipping and storage problems associated with a frozen plasma product. Thawed plasma by the third day of storage has significantly reduced capacity to generate thrombin compared to immediately thawed plasma. This reduced ability to generate thrombin may reduce its efficacy, although clinical relevance of this reduced thrombin generation capacity is unknown (Spinella et al-2015). Third, there is considerable waste with use of frozen plasma products. The 2011 National Blood Collection and Utilization Survey Report (NBCUS) distributed by the US Department of Health and Human Services (HHS) documented 128,759 outdated or processed/unused FFP units and 108,316 total plasma units wasted (HHS-2011). Although this reflects 2.2% of the plasma units processed for transfusion, this translates to approximately $13.4 million, utilizing an average price of FFP reported by hospitals as $58/unit.

5.2. Military Relevance

The deficiencies of the currently licensed frozen plasma products are of particular importance to the military because of their need for a readily available plasma product to treat acutely bleeding patients. A 10-year review of the US Military's Joint Theater Trauma Registry demonstrated the

implementation of damage-control resuscitation (DCR) in the treatment of combat wounded. This strategy focused on providing hemostasis balance to severely injured coagulopathic patients through transfusion with component blood products in a 1:1:1 ratio of FFP to platelets to red blood cells (RBCs) (Pidcoke et al-2012).

In addition to the increased use of FFP as a result of DCR, the military's interest in plasma products, particularly those that can be used in place of FFP, is based upon the costs associated with waste. The uncertainties of combat necessitate the distribution of many more blood products than are actually transfused to ensure adequate supply is available when needed. In comparison to HHS's 2011 NBCUS report based on the civilian population, estimates of military product waste are significantly greater. For example, in support of Operation Iraqi Freedom/Operation New Dawn, of the 141,563 FFP units that were shipped over the decade of 2001-2011, only 64% were ultimately used in transfusion; bag breakage and thawed plasma unit expiration accounted for a large proportion of product waste (Rentas-2012).

The specific problems that the military must address with use of the currently licensed, frozen plasma products include:

- Critical time delays for treatment of an acutely bleeding patient (if thawed plasma is not available) from the time of the start of the patient's resuscitation to the availability of the thawed plasma for infusion due to the time required to thaw the product;
- Problems with shipping a frozen plasma product to remote locations (such as military hospitals) with frequent breakage of the bag (container). The current estimate of the bag breakage rate is approximately 15% of all units shipped, which is much higher than what is reported in the literature for civilian shipments (approximately 3% of shipments) (Gorlin-1995, Hmel et al-2002). This increase is believed to be partly due to the increased number of receiving points in the multi-layered, spoke and hub shipping system that the military must use for distribution;
- Complexities in maintaining freezers and adequate power supply to support a frozen plasma inventory in settings which can be austere;
- Complexities in maintaining licensed plasma thawing devices in settings which can be austere; and
- Increased costs associated with out-dating of frozen or thawed plasma products.

5.3. Rationale for Study

During World War II, freeze dried human plasma was used as an alternative to FFP. It required no refrigeration, was easy to reconstitute, and there were no known reports of lack of efficacy (Kendrick et al-1964). However, the safety of this product was not acceptable due to pathogen transmission. The product was found to transmit Hepatitis B Virus (HBV) because it was manufactured from large (hundreds of donors) plasma pools that were not pathogen inactivated (HHS-2005). The product was withdrawn from use. No supplies of FDP have been available since that time in the United States. Lyophilized plasma (LyP) has been available only through the German Red Cross and French Military on a limited, local basis. Clinical studies on LyP use in Germany and France have not been conducted. A recent Phase 1 clinical study was performed using autologous, reconstituted, LyP in 16 normal, healthy subjects, with evaluation of global

measures of clotting, individual coagulation factor assays, and assessment of adverse events (AEs) (Cancelas et al-2011). There were no SAEs related to product infusion and no occurrence of predetermined AEs including thromboembolic events, infections, evidence of unusual bleeding/bruising, or relevant changes in international normalized ratio or activated partial thromboplastin time (aPTT) during the study. The results indicated no relevant clinical difference between large volumes of FFP and LyP infusions.

Because of the above-listed difficulties with currently licensed plasma products, the US Army Medical Research and Materiel Command (USAMRMC) and Vascular Solutions, Inc. (a wholly owned subsidiary of Teleflex) (VSI) entered into a cooperative research and development agreement to develop a single donor, FDP product that is durably packaged, can be easily stored and transported, is readily reconstituted, and made available for rapid transfusion for military use. In addition, FDP has the potential for much longer storage stability than frozen plasma products. An FDP product that can be reconstituted and used immediately with a long-term shelf-life would virtually eliminate the costs associated with processed but unused or outdated frozen plasma.

Because of these important advantages over currently licensed frozen plasma products, FDP is the highest priority blood-related product in development by the US Military. To improve safety from previous dried plasma products, FDP will be derived from screened, individual blood donors in order to significantly reduce the risk of bloodborne disease transmission and undesired transfusion-associated reaction. Each single-donor unit is tested (per requirements of the blood supply) to reduce the risk of transmission of infectious agents and, hence, will maximize patient safety.

This “first-in-human” Phase 1 study is proposed to assess the safety of infusing reconstituted FDP manufactured for the USAMRMC. The study design incorporates autologous infusions (of both WB and plasmapheresis-derived plasma) and a crossover design to eliminate variables and events known to be related to allogeneic FFP transfusion. The dose of plasma will be increased in each of 3 cohorts for this study to evaluate the safety of escalating doses. The maximum dosage within this study will provide assessment of the safety of infusing large doses of FDP in comparison to FFP. Additionally, this study will evaluate the preservation of key coagulation proteins and factor activities post-infusion, and the effect of different anticoagulants (ACD or CPD) from the use of different starting materials.

5.4. Name and Description of the Investigational Product

RePlas™ FDP is a lyophilized unit of plasmapheresis or WB-derived human plasma product designed for rapid reconstitution. RePlas™ FDP is manufactured from FFP that is frozen at a temperature of -18°C or less within 8 hours of initial collection. To produce RePlas™ FDP, each FFP unit is thawed at a controlled temperature and time. Once thawed, a controlled volume, based on mass, is transferred aseptically into the customized lyophilization bag using a Food and Drug Administration (FDA)-approved tubing welder. The plasma-filled lyophilization bag is frozen at -40°C or less for a minimum of 1 hour and then lyophilized using an established freeze drying cycle. At the end of the drying cycle, the chamber vacuum is broken with a plasma grade carbon dioxide (CO_2) gas to correct for loss of dissolved CO_2 from the starting plasma material during the freeze drying process. In addition, RePlas™ FDP is packaged with an outer foil pouch that is flushed with a fixed amount of CO_2 gas, which results in a near neutral pH in the reconstituted RePlas™ FDP product.

The resulting FDP product is a straw-colored cake that upon reconstitution looks similar in color and consistency to the thawed FFP. FDP is reconstituted prior to use with a commercially available Sterile Water for Injection (SWFI) US Pharmacopeia Convention (USP) that is FDA approved for use as a diluent or solvent in the aseptic preparation of parenteral solutions or as a vehicle for drug administration.

5.5. Summary of Nonclinical and Clinical Trials

5.5.1. Nonclinical Studies

5.5.1.1. Toxicology Testing

FDP is assumed to be active on a species-species basis. Human plasma may cause severe toxicity reactions in animals and is not tolerated at dosages approaching those generally used in humans. Routine toxicology testing in laboratory animals is not considered to contribute any relevant information for the safety and efficacy of FDP in clinical use.

5.5.1.2. Pharmacology

HemCon Medical Technologies, Inc. developed lyophilized swine plasma which was compared with swine FFP in a coagulopathic, multi-trauma swine model (Spoerke et al-2009). Anesthetized, instrumented female pigs (n=32) were studied under conditions of femur fracture, 60% hemorrhage, 30-minute shock period, hypothermia, and Grade 5 liver injury. Clotting factor activity was decreased by an average of 14% in lyophilized swine plasma as determined by pre- and post-lyophilization measurements. Acute blood loss, survival, and heart rate were similar among all groups. Swine resuscitated with lyophilized swine plasma had equivalent or higher mean arterial pressure than those treated with FFP. Both lyophilized swine plasma and FFP, either in combination with RBCs (1:1) or alone, were similar in restoring standard coagulation function: prothrombin time (PT), aPTT, fibrinogen, and thromboelastogram tracings, to baseline values in this dilutional, coagulopathic, poly-trauma swine model. In conclusion, lyophilized swine plasma demonstrated equivalent efficacy to FFP in this swine resuscitation model.

5.5.2. Clinical Studies

Lyophilized, pooled human plasma was used extensively in World War II for resuscitation, but its use was discontinued during the 1950s due to transmission of HBV. In the mid-1980s, the Thai Red Cross undertook a large-scale effort to produce LyP from single units of plasma for use in rural hospitals to meet the need for availability of blood products (Isarangkura et al-1987). Since that time, only the German Red Cross and French Military have developed LyP products, and the use has been limited to the European Union and in theater in places such as Iraq or Afghanistan. Information about the current use of the French LyP product in Iraq and Afghanistan by U.S. Forces is largely anecdotal and clinical studies on the product were not conducted prior to introduction in those settings. Currently, United States Special Operations Command (SOCOM) is working under a special Expanded Access Investigational New Drug (IND) application that approves a joint venture between SOCOM and the French Military at the Centre de Transfusion Sanguine des Armées. This Expanded Access IND allows for the use of a French-developed FDP product in theater in Iraq and Afghanistan. The French-developed FDP has been approved by the French Ministry of Health, but has not been approved by the FDA (Enterprise Information Technology (eIT)-2014).

5.5.2.1. Toxicology in Humans

Based on dried plasma use in World War II and the recent human clinical studies of FDP performed by HemCon Medical Technologies, Inc., there is evidence to suggest that the toxicology of FDP when infused into humans is similar to that of FFP.

It is important to note that RePlas™ FDP has similar levels of citrate compared to FFP. Although, this FDP product, RePlas™ has never been infused into humans, there is considerable information in the literature on the effects of citrate after transfusion of blood products. The additional citric acid in FFP has the potential to slightly increase the risk for citrate toxicity, a risk that is already present and well described in the literature for infusion of large volumes of blood products (Klein and Anstee-2005, Silberman et al-2009).

Harmful effects of citrate infusion may occur if the dosage exceeds 250 mg/kg/hour. Citrate anticoagulant is present in blood or plasma collected and stored for transfusion, and rapid rate of infusion of blood (30 mL/kg/hour) can lead to a decrease in ionized calcium, known as citrate intoxication (Dart-2004). Uncorrected citrate intoxication and the insufficient ionized calcium that ensues can lead to cardiac dysrhythmia, cardiac arrest, tetany, or seizures.

5.5.2.2. Pharmacokinetics and Biological Disposition

The pharmacokinetics and biological disposition of FDP are expected to be the same as FFP.

5.6. Known and Potential Risks and Benefits to Human Subjects

5.6.1. Risks/Discomfort to Subjects and Precautions to Minimize Risk

Outlined below are anticipated and unexpected adverse reactions (ARs), and a brief description of procedures to ameliorate risks and symptoms. All known risks and precautions described here are explained in detail in the informed consent.

5.6.1.1. Venipuncture

Donation of blood and blood products and the collection of blood samples for laboratory testing carries minimal risk of minor discomfort and the possibility of pain/soreness, minor bruising, discoloration, swelling, at the site of the needle puncture and, rarely, the possibility of infection at the needle puncture site.

5.6.1.2. Whole Blood Collection Reactions

Side effects of WB collection include:

- Complications such as a hematoma, redness, nerve damage, arterial puncture, or localized infection at the venipuncture site; and
- Nausea, unpleasant taste, vomiting, light-headedness, fainting, malaise, or seizures.

5.6.1.3. Plasmapheresis Reactions

Side effects of plasmapheresis include:

- Blood loss from the inability to return RBCs during automated plasmapheresis, which may result in:

  - Termination of the procedure; and
  - Deferral from donation for 8 weeks (21 Code of Federal Regulations (CFR) 640.63(e)).
- Complications such as a hematoma or localized infection at the venipuncture site;
- Tingling of lips or fingers or muscle cramping, spasms seizures, tetany, cardiac arrhythmia due to the citrate anticoagulant used in an automated plasmapheresis procedure;
- Allergic reactions such as flushing, itching, hives, abdominal cramps, difficulty breathing, chest pain, or bronchospasm, which may vary in severity from mild to life-threatening;
- Nausea, unpleasant taste, vomiting, light-headedness, fainting, malaise, or seizures; and
- Any other adverse reaction specified by the manufacturer of the automated collection device in its operator's manual or instructions for use.

5.6.1.4. Local Reactions and Systemic Infusion Reactions

Known potential risks associated with allogeneic FFP infusion are well described in the literature. The known risks of FDP infusion are unknown but they are expected to be similar to those associated with the use of FFP. Some of these risks are mitigated by the use of autologous plasma in this study. Subjects receiving FDP are to be monitored during administration and up to 7 days post-infusion for AEs. The expected risks of FDP infusion include:

- Pain at venipuncture site and other venipuncture related ARs;
- Tingling of lips or fingers, muscle cramping, spasms, seizures, or cardiac arrhythmia due to the citrate anticoagulant used during plasma collection;
- Allergic reactions such as flushing, itching, hives, abdominal cramps, difficulty breathing, chest pain, or bronchospasm, which may vary in severity from mild to life-threatening;
- Nausea, unpleasant taste, vomiting, light-headedness, fainting, malaise, or seizures;
- Non-immunologic complications such as the transmission of infectious agents, bacterial sepsis, transfusion-associated circulatory overload, hypothermia-cardiac arrhythmias;
- Metabolic complications such as citrate toxicity-hypocalcemia, acidosis, alkalosis, hyper- or-hypokalemia, and coagulopathies; and
- Hyperventilation.

Other rare side effects that have occurred in patients receiving (1) non-autologous plasma therapy or (2) excess fluid, including their own plasma include:

- Lowered immunity;
- Heart failure;

- Fluid in the lungs causing breathing difficulty;
- Stroke or death;
- Swelling of feet or hands;
- Increase in blood pressure;
- Fever;
- Back pain;
- Redness of urine; and
- Kidney failure.

5.6.1.5. Pregnancy

Risks to unborn babies are unknown at this time; pregnant females will be excluded from this study. Study subjects should not become pregnant for at least 3 months after the last infusion of FDP.

5.6.1.6. Lactation

Risks to nursing infants are unknown at this time; breastfeeding and lactating females will be excluded from this study.

5.6.1.7. Allergic Reaction

As with any IND product administration and no matter what precautions are taken, there is always the risk of a serious, or even life-threatening, allergic reaction. Medical emergency equipment is at the site to handle emergencies, such as anaphylaxis, angioedema, bronchospasm, and laryngospasm.

5.6.1.8. Unknown Risks

Furthermore, as with all research there is the remote possibility of risks that are unknown or that cannot be foreseen based on information that is currently available.

5.6.2. Alternatives to this Investigational New Drug Product or Study

An alternative is to not participate in this study.

5.6.3. Intended Benefit for Subjects

There is no guaranteed benefit for study subjects other than any sense of satisfaction accruing from their contribution to medical science.

5.6.4. Risks to the Study Personnel and the Environment

The principal risks to study personnel involved in this trial are the same as those found in a day-to-day clinical setting (i.e., handling of needles that may be contaminated and the attendant risks including hepatitis, HIV, and other human pathogens). Adherence to standard operating procedures (SOPs) for working with infectious agents and universal precautions will reduce the risk of exposure.

There are no known risks to the environment other than those associated with the generation of biohazardous waste attendant to infusion of humans. All biohazardous waste will be disposed of as stipulated by local, state, and Federal regulations and in accordance with study site SOPs.

5.7. Route of Administration, Dosage Regimen, Treatment Period, and Justification

In this safety study, 3 cohorts of healthy subjects will receive an intravenous (IV) infusion of FDP and/or FFP as follows:

- **Cohort 1:** Eight enrolled subjects will each receive a 1 unit (approximately 270 mL) dose of FDP:
  - **Arm 1** subjects will receive 1 unit (approximately 270 mL) of autologous FDP manufactured from WB. These subjects are expected to make one WB donation. Subjects with a low-volume donation (< 450 mL) may be withdrawn from the study. The site will discard the low-volume donation per their SOP for handling blood and blood products.
  - **Arm 2** subjects will receive 1 unit (approximately 270 mL) of autologous FDP manufactured from plasmapheresis collected FFP. These subjects are expected to undergo one plasmapheresis session. Subjects with a low volume donation (< 500 mL) may be withdrawn from the study. The site will discard the low-volume donation per their SOP for handling blood and blood products.
- **Cohort 2:** Eight enrolled subjects will each receive 2 units (approximately 540 mL) of FDP:
  - **Arm 3** subjects will receive 2 units (approximately 540 mL) of autologous FDP manufactured from WB. These subjects are expected to make two WB donations that are scheduled a minimum of 28-days apart. Subjects with a low-volume donation (< 450 mL) may be withdrawn from the study. The site will discard the low-volume donation per their SOP for handling blood and blood products.
  - **Arm 4** subjects will receive 2 units (approximately 540 mL) of autologous FDP manufactured from plasmapheresis collected FFP. These subjects are expected to undergo one plasmapheresis session. Subjects with a low-volume donation (< 500 mL) may be withdrawn from the study. The site will discard the low-volume donation per their SOP for handling blood and blood products.

    Should an Arm 4 subject require a second plasmapheresis collection attempt, to ensure subject safety, serum protein electrophoresis (SPEP) and STAT total protein will be performed just prior to the subsequent plasmapheresis. If any abnormalities are detected, the subject will be referred to a physician, scheduled for early withdrawal, and replaced with another subject.
- **Cohort 3:** Eight subjects will each receive 2 separate infusion treatments, each dosed at approximately 810 mL. One 810 mL infusion will be with 3 units of autologous FDP and the other approximately 810 mL infusion will be with 3 units of autologous control plasma (FFP). Cohort 3 subjects will be randomized to a product treatment sequence indicating whether their first infusion will be FDP (Arm 5) or FFP (Arm 6).

The starting material for the manufacture of all Cohort 3 FDP units and FFP units will be from autologous plasmapheresis.

- **Arm 5** subjects will receive FDP at their first infusion and FFP at their second infusion; infusion treatments will be separated by a 2-week interval; and
- **Arm 6** subjects will receive FFP at their first infusion and FDP at their second infusion; infusion treatments will be separated by a 2-week interval.

All subjects in Cohort 3 are expected to undergo 3 to 4 plasmapheresis sessions that are each separated by a minimum of 1 week. Subjects who do not meet the minimum volume requirement during plasmapheresis (≥500 mL) may be withdrawn from the study. Low volume collections (< 500 mL) will be discarded per the clinical site's SOP for handling blood and blood products.

As a measure of donor safety, SPEP will be performed on all subjects undergoing the procedure, regardless of assigned cohort/treatment arm. If any abnormalities are detected, the subject will be referred to a physician, scheduled for early withdrawal, and replaced with another subject.

For subjects undergoing multiple plasmapheresis collections, total protein measured by a Beckman Coulter AU analyzer will be performed STAT or up to 24 hours prior to initiating the plasmapheresis. Total protein will only be performed at subsequent plasmapheresis sessions, not during the first collection.

5.8. Compliance Statement

The study will be conducted according to the protocol and in compliance with FDA International Conference on Harmonization (ICH) Good Clinical Practice (GCP), Belmont Principles, and other applicable regulatory and Department of Defense (DoD) requirements. All identified study personnel will be trained to perform their roles and will carry out their responsibilities in accordance with FDA, ICH GCP guidelines, and study site's SOPs. Roles and responsibilities of study staff are presented in Appendix A.

5.9. Study Population

Male and female healthy volunteers who are eligible for WB donation or plasmapheresis donation based on FDA regulations and the AABB donor history questionnaire will be included in this study. Subjects whose only reason for exclusion according to the AABB donor history questionnaire is travel deferral will be accepted. A sample of the complete AABB donor history questionnaire is presented in Appendix B. In addition to the eligibility criteria indicated by the questionnaire, potential subjects must also meet the Inclusion/Exclusion criteria as previously mentioned and later referred to in section 7.4 and section 7.5.

Refer to section 11.2 for a statistical justification of the sample size.

5.10. Study Site

The Hoxworth Blood Center (HBC) is an academic blood center that provides daily blood and cell therapy product needs to the whole community of the Greater Cincinnati area which is populated by approximately 1.9 million inhabitants. Cincinnati is located in Southwestern Ohio and is highly diverse with a population mostly composed of European (German, Irish, Italian,

and Jewish) and African background inhabitants. HBC processes approximately 80,000 blood units a year and approximately 10,000 platelets apheresis a year. It routinely produces plasma products from WB and plasmapheresis procedures for the community and provides immunohematology reference laboratory services and transplantation immunology services for the Greater Cincinnati area hospitals. The HBC/University of Cincinnati research program is extremely active in the development and validation of innovative products in transfusion medicine and cell therapies. The center is located central to the University Medical campus, at a 1 to 5 minute walking distance to the major hospitals and facilities of the University. The HBC has the personnel, expertise, and equipment necessary to perform this study, including blood donation staff, plasmapheresis devices, expert nurses in the field of plasmapheresis, and on-call doctor. The work is supervised and directed by Dr. Jose A. Cancelas, MD, PhD, who is Professor of Pediatrics and Deputy Director of the Blood Center, and who will be in charge of the medical aspects of the study. The HBC is uniquely qualified given its long-term experience in the development of clinical research trials in blood banking involving healthy volunteers and collection/infusion of large amounts of blood derived cell/plasma products.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this study is to assess the safety of single infusions with the RePlas™ FDP product at increasing fixed doses of either 1 unit (approximately 270 mL), 2 units (approximately 540 mL), or 3 units (approximately 810 mL) in normal healthy subjects. In the 2 lower dose cohorts, safety will also be assessed in terms of the type of autologous plasma used as the starting material in the manufacture of the investigational product:

- FDP derived from WB where CPD was used as the anticoagulant, or FDP-CPD; and
- FDP collected by plasmapheresis where ACD was used as the anticoagulant, or FDP-ACD.

The highest dose cohort will receive FDP manufactured only from FFP collected by plasmapheresis (FDP-ACD). Conclusions on whether the study meets its safety objectives will be based only on treatment emergent adverse events (TEAEs). These are adverse events (AEs) that occur after treatment (plasma infusion) has begun and throughout the study's post-infusion follow-up period.

6.2. Secondary Objectives

The secondary objectives are to:

- Assess the safety of a fixed-dose infusion of 3 FDP units (approximately 810 mL) in comparison to infusion with the same dose of autologous FFP collected during plasmapheresis; and
- Determine if the changes in specific coagulation factors, hematology, and chemistry values are similar within clinically meaningful levels after infusion of either 3 units of autologous FDP or FFP.

6.3. Trial Design

The following sections describe information and procedures involving study subjects. Additional, detailed information will be explained in the study's Manual of Procedures (MOP).

6.4. Study Endpoints

6.4.1. Primary Endpoints

The primary endpoints to assess safety are TEAEs; SAEs; Suspected, Unexpected, Serious Adverse Reactions (SUSARs); and death.

6.4.2. Secondary Endpoints

The following secondary endpoints will only be evaluated in Cohort 3 subjects:

- Change in pre- and post-infusion values for Prothrombin Time and International Normalized Ratio (PT/INR), aPTT, Factors I, II, V, VII, VIII, IX, X, XI, D-DIMER, von Willebrand Factor activity, Protein S activity, Protein C activity, Prothrombin

Fragments 1+2 (PF 1+2), Thrombin/Antithrombin (TAT), Antithrombin III (AT-III), Alpha-2 antiplasmin, and C3a des Arg activity compared to pre-infusion values after infusion of 3 units of FDP compared to 3 units of FFP; and

- Determine if the changes in specific hematology, urinalysis, vital signs, DAT, and chemistry values are similar within clinically meaningful levels after infusion of either 3 units of autologous FDP or FFP.

6.5. Overall Study Design

This single-site, partial double-blind study in healthy volunteers is designed to assess the safety of infusing ascending doses of reconstituted autologous FDP in 3 fixed-dose cohorts. Subjects in Cohort 1 will receive 1 unit of FDP, which is approximately 270 mL. Subjects in Cohort 2 will receive 2 FDP units, which total approximately 540 mL. Cohorts 1 and 2 are the lower-dose cohorts. Subjects will be assigned to these beginning with the lowest dose, Cohort 1. In the absence of TEAEs, SAEs or the implementation of protocol stopping rules (SRs), and with Data and Safety Monitoring Board (DSMB) recommendation and Sponsor approval subjects assigned to Cohort 2 will be infused with an increased dose of 2 units. For both of these cohorts subjects will also be assigned to 1 of 2 single infusion treatment arms:

1. Infusion of FDP manufactured with autologous plasma derived from WB (FDP-CPD), at the corresponding dose; or
2. Infusion of FDP manufactured with autologous plasma collected by plasmapheresis (FDP-ACD), at the corresponding dose.

In the absence of TEAEs, SAEs, or the implementation of protocol stopping rules (SRs) in Cohort 2 subjects, infusions in Cohort 3 subjects may be implemented. Cohort 3 is designed as a randomized, controlled, crossover infusion of 3 units of FDP (approximately 810 mL) and 3 units of FFP (approximately 810 mL) at separate visits. Subjects are randomized to a specific infusion schedule of either 3 units of FDP or 3 units of FFP at the first infusion visit, followed by infusion with the alternate product at the second infusion visit. Crossover of FDP and FFP enables comparison of infusion safety and select coagulation factor recoveries within the same subjects between FDP and FFP at this higher dose. Unlike Cohorts 1 and 2, the FDP and FFP infusion products in Cohort 3 are sourced solely from autologous plasmapheresis donations (FDP-ACD). A 2-week period between infusion visits is required for all Cohort 3 subjects regardless of infusion schedule.

Use of autologous plasma in the trial assists in the elimination of potential AEs related to allogeneic plasma infusion, but it also adds additional burden to participating subjects who, upon consent and enrollment, need to donate sufficient volume of plasma to provide the autologous plasma needed for the trial infusions (eg, manufacture of autologous FDP units in all cohorts; in Cohort 3, the additional need for FFP in addition to FDP). Blood donation standards typically require a 56-day interval between WB donations; however, a shortened study donation period of a minimum of 28 days between WB donations will be used for study subjects. Without the loss of RBCs in plasmapheresis, these types of donations can be made more frequently, with a minimum of 7 days between donations. Plasmapheresis donations yield up to 800 mL plasma depending on donor size. Thus, the trial's overall design and use of plasmapheresis alone in Cohort 3 reduces the frequency in which subjects will need to donate due to significantly larger estimated plasma volumes per donation. Plasmapheresis offers practical advantages and using

FDA's guidance regarding automated plasma collection volumes, reduces potential safety implications (FDA-1992).

Subjects in Cohorts 1 and 2 will provide sufficient plasma volume for a single infusion with either 1 or 2 units, respectively. Based on assigned treatment arm, subjects will provide plasma through either WB or plasmapheresis collection for manufacture of autologous FDP-CPD or FDP-ACD. Cohort 2 subjects in the FDP-CPD treatment arm are required to successfully make 2 WB donations within a relatively short period of time to provide adequate volume for their use in the trial. Because of the extraordinarily long time required to accrue sufficient WB-derived plasma for the high dose cohort (approximately 11 months), the FDP-CPD treatment arm is not included in Cohort 3. The total starting volume of plasma needed from each Cohort 3 subject is approximately 1620 mL; triple that of Cohort 2 and thus inclusion of this treatment arm in Cohort 3 would require 6 WB donations, increasing subject risk for significant iron store depletion and anemia. Table 3 provides details on assigned cohorts and treatment arms as well as indicates the type, frequency, and total volume of blood/plasma donations required.

Table 3: Cohort and Treatment Arm Details

Dose Cohorts and Treatment Arms	Number of Subjects	Donation Type	Approximate Volume Autologous Plasma Required	Number of Donations
Cohort 1: One unit single infusion [approximately 270 mL]				
Arm 1: FDP-CPD	4	WB	270	1
Arm 2: FDP-ACD	4	Plasmapheresis	270	1
Cohort 2: Two units single infusion [approximately 540 mL]				
Arm 3: FDP-CPD	4	WB	540	2
Arm 4: FDP-ACD	4	Plasmapheresis	540	1
Cohort 3: Three units crossover infusion [approximately 810 mL, each]				
Arm 5: FDP ACD x FFP	4	Plasmapheresis	1,620	3-4[1]
Arm 6: FFP x FDP ACD	4	Plasmapheresis	1,620	3-4[1]

The following SRs will be applied to all study subjects throughout the trial:

1. An SAE that is determined to be possibly, probably, or definitely related to the study product;
2. An AE related to the study product that the PI, RM, and/or sponsor's PVG MD agree jeopardizes the subject's health or safety;
3. An AE related to the study product that requires medical or surgical intervention to prevent occurrence of an SAE;
4. A post-infusion, abnormal coagulation function assay which is also a greater than 20% change from baseline for PT/INR and/or aPTT values (eg, a subject who has a baseline INR of 1.0 with a post-infusion INR of 1.3 will activate an SR, because this is an

abnormal coagulation function assay result that is also a greater than 20% change from the pre-infusion assay result); and/or

5. Post-infusion development of hemolysis or deep vein thrombosis (DVT), cardiac ischemia, or pulmonary embolism (PE). DVT will be determined following the Institute for Clinical Systems Improvement (ICSI) Health Care Guideline: Venous Thromboembolism Diagnosis and Treatment (includes assessment of D-Dimer results and Wells criteria ≥ 2) (Dupras et al-2013).

If any of the above conditions occur, the study will be paused to assess continuation of the study.

The DSMB will convene after completion of each cohort. DSMB meetings will be scheduled to maximize the amount of subject data reported to the DSMB through the 28-day follow-up visit. The DSMB will have at a minimum all data through the 7-Day Follow-Up Visit. Following each meeting, the DSMB will provide the sponsor with a recommendation about proceeding with infusions in the subsequent cohort. Following the review of Cohort 3 data, the DSMB will provide a recommendation about proceeding with the next planned FDP trial. After the receipt and consideration of a DSMB recommendation, the sponsor will make a final determination about proceeding to the next cohort or the next FDP trial. It is up to the sponsor to make a final determination on how to proceed.

Table 4: Study Events Schedule for Cohort 1, Arms 1 and 2

Visit Activities:	Visit 1	Visit 2	Visit 3	Visit 4	Phone Calls[L]	Visit 5	Phone Call[L]	Visit 6
	Screening	WB/Plasmapheresis Collection	Infusion	24-Hour Follow-Up	48 & 72 hrs	7-Day Follow-Up	14-Day	28-Day Follow-Up
Study Day*:	**-56 to -49**	**-35**	**1**	**2**	**3 & 4**	**8**	**15**	**29**
Visit Window:				**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 2 hrs**	**± 1 day**
General Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Demographic Questionnaire	X							
AABB Donor History Questionnaire[A]	X	X						
Duke Activity Status Index	X							
Subject Medical Health Standardized Questionnaire[B]	X	X	X	X		X		X
Complete Physical Exam[C]	X		X	X				
Abbreviated Physical Exam[D]		X				X		X
Wells Scale[H]	X		X	X				
Vital Signs[E]	X	X	X[H]	X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X
Blood/Plasma Collection[F]		X						
FDP Infusion			X					
Visual Inspection of Blood Components		X	X					
Exit Interview[G]								X
Laboratory Tests								
Urine Drug Screening	X							
Urine Pregnancy Test (females only)	X		X[K]					
Urinalysis	X		X[K]	X				
Chemistry Panel[I]	X		X[K]	X		X		
Complete Blood Count (CBC)[J]	X		X[K]	X		X		X
Hematocrit		X						
PT/INR, aPTT	X		X[K]	X				X

Table 4: Study Events Schedule for Cohort 1, Arms 1 and 2 (continued)

Visit Activities:	Visit 1	Visit 2	Visit 3	Visit 4	Phone Calls[L]	Visit 5	Phone Call[L]	Visit 6
	Screening	WB/Plasmapheresis Collections	Infusion	24-Hour Follow-Up	48 & 72 hrs	7-Day Follow-Up	14-Day	28-Day Follow-Up
Study Day*:	**-56 to -49**	**-35**	**1**	**2**	**3 & 4**	**8**	**15**	**29**
Visit Window:				**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 2 hrs**	**± 1 day**
Direct Antiglobulin Test (DAT) (Immunoglobulin G (IgG) and Complement Factor 3 (C3))	X		X[K]	X				X
D-Dimer Test	X		X[K]	X				
Blood Type for ABO and Rh	X		X[K]					
Red-Cell Antibody Screen	X							
Syphilis Screen	X							
HTLV Antibody Screening Test	X							
HIV-1/2, HBV, HCV, and West Nile Virus Nucleic Acid Tests	X							
Cross-match RBC vs FDP			X[K]					
Reverse Type of FDP			X[K]					
SPEP[M]		X						

*The estimated manufacturing time is 5 weeks.

[A] The AABB donor history questionnaire is administered at all donation visits.

[B] Confirm data are accurate; subject is healthy with no significant medical history change.

[C] Complete physical exams to include height (screening only), weight, vital signs[E], and a targeted assessment of health as described in section 7.2 and section 8.2.

[D] Abbreviated physical exam to include vital signs[E] and a general assessment of health.

[E] Vital signs monitored include blood pressure, heart rate, respiration rate, and temperature. These will be measured every 15 minutes (± 5 minutes) during the infusion, every 30 minutes (± 5 minutes) between 0 and 4 hours post-infusion, and then every 4 hours (±40 minutes) until the subject is released from the clinic.

[F] Blood and plasma collection will generally be done approximately 5 weeks before the study infusion in order to allow sufficient time for product preparation, testing, release, and shipment back to the site.

[G] Exit interview may take place at any point during the study and is dependent upon subject's continued enrollment status.

[H] Monitor vital signs every 15 minutes during infusion; every 30 minutes for up to 4 hours post-infusion; and after 6 hours, vital signs should be measured every 4 hours until the subject is released. Subjects assessed for DVT, PE, and cardiac ischemia using the Wells Scale prior to infusion, at 30 minutes, 4 hours, and 24 hours post-infusion before the subject can be released from the clinic.

[I] Chemistry panel includes Calcium, Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Bicarbonate, Chloride, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN), Lactate, and Creatinine. The chemistry panel also includes pH, Ionized Calcium, and Total Magnesium, which will only be measured at pre-infusion and 0.5 hour post-infusion.

[J] CBC comprises Hematocrit, Hemoglobin, Platelet Count, RBC Count, and White Blood Cell (WBC) Count.

[K] See Table 7 – Laboratory Testing Schedule and Volumes for Cohorts 1 and 2 for laboratory testing details. [L]

Follow-up phone calls to the subject will be made 48 hours, 72 hours, and 14 days post infusion.

[M] SPEP performed for subjects undergoing plasmapheresis only.

Table 5: Study Events Schedule for Cohort 2, Arm 3

Visit Activities:	**Visit 1**	**Visits 2a/2b**	**Visit 3**	**Visit 4**	**Phone Calls[L]**	**Visit 5**	**Phone Call[L]**	**Visit 6**
	Screening	**WB Collections**	**Infusion**	**24-Hour Follow-Up**	**48 & 72 hrs**	**7-Day Follow-Up**	**14-Day**	**28-Day Follow-Up**
Study Day*:	**-84 to -77**	**-63 to -35**	**1**	**2**	**3 & 4**	**8**	**15**	**29**
Visit Window:				**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 2 hrs**	**± 1 day**
General Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Demographic Questionnaire	X							
AABB Donor History Questionnaire [A]	X	X						
Duke Activity Status Index	X							
Subject Medical Health Standardized Questionnaire [B]	X	X	X	X		X		X
Complete Physical Exam [C]	X		X	X				
Abbreviated Physical Exam [D]		X				X		X
Wells Scale[H]	X		X	X				
Vital Signs [E]	X	X	X[H]	X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X
Blood Collection[F]		X						
SPEP[F]		X						
FDP Infusion			X					
Visual Inspection of Blood Components		X	X					
Exit Interview[G]								X
Laboratory Tests								
Urine Drug Screening	X							
Urine Pregnancy Test (females only)	X		X[K]					
Urinalysis	X		X[K]	X				
Chemistry Panel[I]	X		X[K]	X		X		
CBC[J]	X		X[K]	X		X		X
Hematocrit		X						
PT/INR, aPTT	X		X[K]	X				X
DAT (IgG and C3)	X		X[K]	X				X
D-Dimer Test	X		X[K]	X				
Blood Type for ABO and Rh	X		X[K]					

Table 5:Study Events Schedule for Cohort 2, Arm 3 (continued)

Visit Activities:	Visit 1	Visits 2a/2b	Visit 3	Visit 4	Phone Calls[L]	Visit 5	Phone Call[L]	Visit 6
	Screening	WB Collections	Infusion	24-Hour Follow-Up	48 & 72 hrs	7-Day Follow-Up	14-Day	28-Day Follow-Up
Study Day*:	**-84 to -77**	**-63 to -35**	**1**	**2**	**3 & 4**	**8**	**15**	**29**
Visit Window:				**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 2 hrs**	**± 1 day**
Red-Cell Antibody Screen	X							
Syphilis Screen	X							
HTLV Antibody Screening Test	X							
HIV-1/2, HBV, HCV, and West Nile Virus Nucleic Acid Tests	X							
Cross-match RBC vs FDP			X[K]					
Reverse Type of FDP			X[K]					

[*]The estimated manufacturing time is 5 weeks.
[A]The AABB donor history questionnaire is administered at all donation visits.
[B]Confirm data are accurate; subject is healthy with no significant medical history change.
[C]Complete physical exams to include height (screening only), weight, vital signs[E], and a targeted assessment of health as described in section 7.2 and section 8.2
[D]Abbreviated physical exam to include vital signs[E] and a general assessment of health.
[E]Vital signs monitored include blood pressure, heart rate, respiration rate, and temperature. These will be measured every 15 minutes (± 5 minutes) during the infusion, every 30 minutes (± 5 minutes) between 0 and 4 hours post-infusion, and then every 4 hours (± 40 minutes) until the subject is released from the clinic.
[F]Blood and plasma collections will generally be done approximately 5 weeks before the study infusion in order to allow sufficient time for product preparation, testing, release, and shipment back to the clinical site. Arm 3 requires 2 WB donations. SPEP only performed for subjects undergoing plasmapheresis.
[G]Exit interview may take place at any point during the study and is dependent upon subject's continued enrollment status.
[H]Monitor vital signs every 15 minutes during infusion; every 30 minutes for up to 4 hours post-infusion; and after 6 hours, vital signs should be measured every 4 hours until the subject is released. Subjects assessed for DVT, PE, and cardiac ischemia using the Wells Scale prior to infusion, at 30 minutes, 4 hours, and 24 hours post-infusion before the subject can be released from the clinic.
[I]Chemistry panel includes Calcium, ALP, ALT, AST, Bicarbonate, Chloride, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, BUN, Lactate, and Creatinine. pH, Ionized Calcium and Total Magnesium will only be measured at pre-infusion and 0.5 hour post-infusion.
[J]CBC comprises Hematocrit, Hemoglobin, Platelet Count, RBC Count, and WBC Count.
[K]See Table 7 - Laboratory Testing Schedule and Volumes for Cohorts 1 and 2 for laboratory testing details.
[L] Follow-up phone calls to the subject will be made 48 hours, 72 hours, and 14 days post infusion.

Table 6: Study Events Schedule for Cohort 2, Arm 4

Visit Activities:	Visit 1	Visit 2	Visit 3	Visit 4	Phone Calls[L]	Visit 5	Phone Call[L]	Visit 6
	Screening	Plasmapheresis Collection	Infusion	24-Hour Follow-Up	48 & 72 hrs	7-Day Follow-Up	14-Day	28-Day Follow-Up
Study Day*:	**-56 to -49**	**-45 to -35**	**1**	**2**	**3 & 4**	**8**	**15**	**29**
Visit Window:				**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 2 hrs**	**± 1 day**
General Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Demographic Questionnaire	X							
AABB Donor History Questionnaire[A]	X	X						
Duke Activity Status Index	X							
Subject Medical Health Standardized Questionnaire[B]	X	X	X	X		X		X
Complete Physical Exam[C]	X		X	X				
Abbreviated Physical Exam[D]		X				X		X
Wells Scale[H]	X		X	X				
Vital Signs[E]	X	X	X[H]	X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X
Plasma Collection[F]		X						
FDP Infusion			X					
Visual Inspection of Blood Components		X	X					
Exit Interview[G]								X
Laboratory Tests								
Urine Drug Screening	X							
Urine Pregnancy Test (females only)	X		X[K]					
Urinalysis	X		X[K]	X				
Chemistry Panel[I]	X		X[K]	X		X		
CBC[J]	X		X[K]	X		X		X
Hematocrit		X						
PT/INR, aPTT	X		X[K]	X				X
DAT (IgG and C3)	X		X[K]	X				X
D-Dimer Test	X		X[K]	X				
Blood Type for ABO and Rh	X		X[K]					

Table 6: Study Events Schedule for Cohort 2, Arm 4 (continued)

Visit Activities:	Visit 1	Visit 2	Visit 3	Visit 4	Phone Calls[L]	Visit 5	Phone Call[L]	Visit 6
	Screening	Plasmapheresis Collection	Infusion	24-Hour Follow-Up	48 & 72 hours	7-Day Follow-Up	14-Day	28-Day Follow-Up
Study Day*:	**-56 to -49**	**-45 to -35**	**1**	**2**	**3 & 4**	**8**	**15**	**29**
Visit Window:				**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 2 hrs**	**± 1 day**
Red-Cell Antibody Screen	X							
Syphilis Screen	X							
Screening Test for HTLV Antibody	X							
Nucleic Acid Tests for HIV-1/2, HBV, HCV, and West Nile Virus	X							
Cross-match RBC vs. FDP/FFP			X[K]					
Reverse Type of FDP/FFP			X[K]					
SPEP[M]		X						

*The estimated manufacturing time is 5 weeks.

[A]The AABB donor history questionnaire is administered at all donation visits.

[B]Confirm data are accurate; subject is healthy with no significant medical history change.

[C] Complete physical exams to include height (screening only), weight, vital signs[E], and a targeted assessment of health as described in section 7.2 and section 8.2.

[D]Abbreviated physical exam to include vital signs[E] and a general assessment of health.

[E]Vital signs monitored include blood pressure, heart rate, respiration rate, and temperature. These will be measured every 15 minutes (± 5 minutes) during the infusion, every 30 minutes (± 5 minutes) between 0 and 4 hours post-infusion, and then every 4 hours (± 40 minutes) until the subject is released from the clinic.

[F]Blood and plasma collections will generally be done approximately 5 weeks before the study infusion in order to allow sufficient time for product preparation, testing, release, and shipment back to the clinical site. Cohort 2, Arm 4 subjects are expected to undergo 1 plasmapheresis procedure.

[G]Exit interview may take place at any point during the study and is dependent upon subject's continued enrollment status.

[H]Monitor vital signs every 15 minutes during infusion; every 30 minutes for up to 4 hours post-infusion; and after 6 hours, vital signs should be measured every 4 hours until the subject is released. Subjects assessed for DVT, PE, and cardiac ischemia using the Wells Scale prior to infusion, at 30 minutes, 4 hours, and 24 hours post-infusion before the subject can be released from the clinic.

[I]Chemistry panel includes Calcium, ALP, ALT, AST, Bicarbonate, Chloride, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, BUN, Lactate, and Creatinine. pH, Ionized Calcium and Total Magnesium will only be measured at pre-infusion and 0.5 hour post-infusion.

[J]CBC comprises Hematocrit, Hemoglobin, Platelet Count, RBC Count, and WBC Count.

[K]See Table 7 - Laboratory Testing Schedule and Volumes for Cohorts 1 and 2 for laboratory testing details.

[L] Follow-up phone calls to the subject will be made 48 hours, 72 hours, and 14 days post infusion.

[M] SPEP performed for subjects undergoing plasmapheresis. Total Protein will be performed STAT or up to 24 hours prior to plasmapheresis if a subject requires multiple collections.

Table 7: Laboratory Testing Schedule and Volumes for Cohorts 1 and 2

Laboratory Testing	Screening	Donation Visits	Infusion Visit – Cohorts 1 and 2			24-Hour Follow-Up	Day 7 Follow-Up	Day 28 Follow-Up
			Pre-Infusion	Post-Infusion				
				0.5 hr	4 hrs			
Urine Pregnancy Test (females only)	X		X					
Urine Drug Screening	X							
Urinalysis	X		X	X	X	X		
Chemistry Panel[A]	X		X	X	X	X	X	
CBC[B]	X		X	X	X	X	X	X
Hematocrit		X						
PT/INR	X		X	X	X	X		X
aPTT	X		X	X	X	X		X
DAT (IgG and C3)	X		X			X		X
D-Dimer	X		X	X[E]	X[E]	X		
Blood Type for ABO and Rh	X		X[C]					
Red-Cell Antibody Screen	X							
Syphilis Screen	X							
Screening Test for HTLV Antibody	X							
Nucleic Acid Tests for HIV-1/2, HBV, HCV, and West Nile Virus	X							
Cross-match RBC			X					
Reverse Type FDP			X					
WB/Plasma Collection		X						
SPEP		X[F]						
Total Blood Volume Collected	**~51mL**	**500 mL-607 mL[D]**	**~36mL**	**~36mL**	**~30 mL**	**~34mL**	**~21mL**	**~20 mL**

[A]Chemistry panel includes Calcium, ALP, ALT, AST, Bicarbonate, Chloride, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, BUN, Lactate, and Creatinine. pH, Ionized Calcium and Total Magnesium will only be measured at pre-infusion and 0.5 hour post-infusion.
[B]CBC comprises Hematocrit, Hemoglobin, Platelet Count, RBC Count, and WBC Count.
[C]ABO only at the pre-infusion sampling time.
[D]Collection volume range for this visit includes the WB (approximately 500 mL) or plasma donation volume (approximately 600 mL) collected at each visit. [E]D-Dimer collection at 30 minutes and 4 hours post-infusion must be done STAT. Results must be received and reviewed by the PI prior to the subject's release from the clinic.
[F]SPEP is performed for Cohort 2, Arm 4 subjects at each plasmapheresis session. Total Protein will be performed STAT or up to 24 hours prior to plasmapheresis if a subject requires multiple collections.

Table 8: Study Events Schedule for Cohort 3

Visit Activities:	**Visit 1**	**Visits 2a-2d[P]**	**Visit 3**	**Visit 4**	**Phone Calls [N]**	**Visit 5**	**Visit 6**	**Visit 7**	**Phone Calls [N]**	**Visit 8**	**Phone Call [N]**	**Visit 9**
	Screening	**Plasmapheresis Collections**	**Infusion #1**	**24-Hour Follow-Up**	**48 & 72 hrs**	**7-Day Follow-Up**	**Infusion #2**	**24-Hour Follow-Up**	**48 & 72 hrs**	**7-Day Follow-Up**	**14-Day**	**28-Day Follow-Up**
Study Day*:	**-56 to -49**	**-55 to -35**	**1**	**2**	**3 & 4**	**8**	**15**	**16**	**17 & 18**	**22**	**29**	**43**
Visit Window:				**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 3 days**	**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 2 hrs**	**± 1 day**
General Procedures												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographic Questionnaire	X											
AABB Donor History Questionnaire[A]	X	X										
Duke Activity Status Index	X											
Subject Medical Health Standardized Questionnaire[B]	X	X	X	X		X	X	X		X		X
Complete Physical Exam[C]	X		X	X								
Randomization			X									
Abbreviated Physical Exam[D]		X				X	X	X		X		X
Wells Scale[H]	X		X	X			X	X				
Vital Signs[E]	X	X	X[H]	X		X	X[H]	X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X	X	X	X	X
Plasma Collection[F]		X										

Table 8: Study Events Schedule for Cohort 3 (continued)

Visit Activities:	**Visit 1**	**Visits 2a-2d[P]**	**Visit 3**	**Visit 4**	**Phone Calls [N]**	**Visit 5**	**Visit 6**	**Visit 7**	**Phone Calls [N]**	**Visit 8**	**Phone Call [N]**	**Visit 9**
	Screening	**Plasmapheresis Collections**	**Infusion #1**	**24-Hour Follow-Up**	**48 & 72 hrs**	**7-Day Follow-Up**	**Infusion #2**	**24-Hour Follow-Up**	**48 & 72 hrs**	**7-Day Follow-Up**	**14-Day**	**28-Day Follow-Up**
Study Day*:	**-56 to -49**	**-55 to -35**	**1**	**2**	**3 & 4**	**8**	**15**	**16**	**17 & 18**	**22**	**29**	**43**
Visit Window:				**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 3 days**	**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 2 hrs**	**± 1 day**
Visual Inspection of Blood Components		X	X				X					
FDP/FFP Infusion			X				X					
Exit Interview[G]												X
Laboratory Tests												
Urine Drug Screening	X											
Urine Pregnancy Test (females only)	X		X[J]				X[J]					
Urinalysis	X		X[J]	X			X[J]	X				
Chemistry Panel[I]	X		X[J]	X		X	X[J]	X		X		
CBC[K]	X		X[J]	X		X	X[J]	X		X		X
Hematocrit		X										
PT/INR, aPTT	X		X[J]	X			X[J]	X				X
DAT (IgG and C3)	X		X[J]	X			X[J]	X				X
SPEP		X[L]										
Blood Type for ABO and Rh	X		X[J]				X[J]					
Red-Cell Antibody Screen	X											
Syphilis Screen	X											
HTLV Antibody Screening Test	X											

Table 8: Study Events Schedule for Cohort 3 (continued)

Visit Activities:	**Visit 1**	**Visits 2a-2d[P]**	**Visit 3**	**Visit 4**	**Phone Calls [N]**	**Visit 5**	**Visit 6**	**Visit 7**	**Phone Calls [N]**	**Visit 8**	**Phone Call [N]**	**Visit 9**
	Screening	**Plasmapheresis Collections**	**Infusion #1**	**24-Hour Follow-Up**	**48 & 72 hrs**	**7-Day Follow-Up**	**Infusion #2**	**24-Hour Follow-Up**	**48 & 72 hrs**	**7-Day Follow-Up**	**14-Day**	**28-Day Follow-Up**
Study Day*:	**-56 to -49**	**-55 to -35**	**1**	**2**	**3 & 4**	**8**	**15**	**16**	**17 & 18**	**22**	**29**	**43**
Visit Window:				**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 3 days**	**± 3 hrs**	**± 2 hrs**	**± 1 day**	**± 2 hrs**	**± 1 day**
HIV-1/2, HBV, HCV, & West Nile Virus Nucleic Acid Tests	X											
Cross-match RBC vs. FDP/FFP			X				X					
Reverse Type of FDP/FFP			X				X					
Coagulation Factor Tests[M]			X[J]				X[J]					
D-Dimer Test	X		X[J]	X			X[J]	X				
Total Protein [O]		X					X[J]					
PF 1+2, TAT, AT-III, Alpha-2 Antiplasmin, and C3a des Arg[Q]			X[J]				X[J]					

[*]The estimated manufacturing time is 5 weeks.
[A]The AABB donor history questionnaire is administered at all donation visits.
[B]Confirm data are accurate; subject is healthy with no significant medical history change.
[C] Complete physical exams to include height (screening only), weight, vital signs[E], and a targeted assessment of health as described in section 7.2 and section 8.2.
[D]Abbreviated physical exam to include vital signs [E] and a general assessment of health.
[E]Vital signs monitored are blood pressure, heart rate, respiration rate, and temperature. These will be measured every 15 minutes (± 5 minutes) during the infusion, every 30 minutes (± 5 minutes) between 0 and 4 hours post-infusion, and then every 4 hours (± 40 minutes) until the subject is released from the clinic.
[F]Each plasmapheresis session is to be scheduled approximately 7-10 days apart. Cohort 3 will require 3 to 4 plasma donation sessions.
[G]Exit interview may take place at any point during the study and is dependent upon subject's continued enrollment status.

[H]Monitor vital signs every 15 minutes during infusion; every 30 minutes for up to 4 hours post-infusion; and after 6 hours, vital signs should be measured every 4 hours until the subject is released. Subjects assessed for DVT, PE, and cardiac ischemia using the Wells Scale prior to infusion, at 30 minutes, 4 hours, and 24 hours post-infusion before the subject can be released from the clinic.

[I]Chemistry panel includes Calcium, ALP, ALT, AST, Bicarbonate, Chloride, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, BUN, Lactate, and Creatinine. pH, Ionized Calcium and Total Magnesium will only be measured at pre-infusion and 0.5 hour post-infusion.

[J]See Table 9 - Laboratory Testing Schedule and Volumes for Cohort 3 for sampling time points.

[K]CBC comprises Hematocrit, Hemoglobin, Platelet Count, RBC Count, and WBC Count.

[L]SPEP is performed on the donated plasma at each plasmapheresis visit.

[M]Coagulation testing for Factors I, II, V, VII, VIII, IX, X, XI von Willebrand Factor activity, and Total Protein C and S activity.

[N] Follow-up phone calls to the subject will be made 48 hours and 72 hours following both Infusion Visits. The 14-day follow-up phone call will only occur after Infusion Visit #2.

[O] Total Protein can be performed up to 24 hours prior to each subsequent plasmapheresis session.

[P] Additional collection visits may be required in the event that a plasma unit experiences an issue during preparation (eg, leakage during transfer to lyophilization bag) or during lyophilization (eg, bag breakage during freeze-drying).

[Q] These tests are for research purposes only and will not be used to manage the safety of study participants.

Table 9: Laboratory Testing Schedule and Volumes for Cohort 3

Laboratory and Coagulation Factor Testing	Screening	Collection Visits	Infusion Visits #1 and #2			24-Hour Follow-Up Visits	7-Day Follow-Up Visits	28-Day Follow-Up Visit
			Pre-Infusion	Post-Infusion				
				0.5 hr	4 hrs			
Pregnancy Test (females only)	X		X					
Urine Drug Screening	X							
Urinalysis	X		X	X	X	X		
Chemistry Panel[A]	X		X	X	X	X	X	
CBC[B]	X		X	X	X	X	X	X
Hematocrit		X						
PT/INR	X		X	X	X	X		X
aPTT	X		X	X	X	X		X
DAT (IgG and C3)	X		X			X		X
Blood Type for ABO and Rh	X		X[C]					
Red-Cell Antibody Screen	X							
Syphilis Screen	X							
HTLV Antibody Screening Test	X							
HIV-1/2, HBV, HCV, and West Nile Virus Nucleic Acid Tests	X							
Cross-match RBC			X					
Reverse Type FDP/FFP			X					
Coagulation Factor Tests[D]			X	X	X			
D-Dimer Test	X		X	X[F]	X[F]	X		
Total Protein [G]		X						
PF 1+2, TAT, AT-III, Alpha-2 Antiplasmin, and C3a des Arg			X	X				
Plasma Collection		X						
SPEP[G]		X						
Total Blood Volume Collected	**~51mL**	**~607mL[E]**	**~68mL**	**~64mL**	**~58mL**	**~34mL**	**~21mL**	**~20 mL**

[A]Chemistry panel includes Calcium, ALP, ALT, AST, Bicarbonate, Chloride, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, BUN, Lactate, and Creatinine. pH, Ionized Calcium and Total Magnesium will only be measured at pre-infusion and 0.5 hour post-infusion.
[B]CBC comprises Hematocrit, Hemoglobin, Platelet Count, RBC Count, and WBC Count.
[C]ABO only at this time point.
[D]Coagulation testing for Factors I, II, V, VII, VIII, IX, X, XI, von Willebrand factor activity, and Protein C and S activity.
[E]Collection volume for this visit includes the plasma donation volume (approximately 600 mL plasma collected at each visit).
[F]D-Dimer collection at 30 minutes and 4 hours post-infusion must be done STAT. Results must be received and reviewed by the PI prior to the subject's release from the clinic.

[G]SPEP is performed for subjects at each plasmapheresis session. Total Protein will be performed STAT or up to 24 hours prior to plasmapheresis at each subsequent plasmapheresis session.

6.6. Measures Taken to Minimize/Avoid Bias

6.6.1. Randomization

Subjects in Cohorts 1 and 2 will not be randomized. The list of WB and plasmapheresis donors who have previously indicated an interest in participating in research will be sorted by donation type. The center will work through the list using a systematic scheme that represents a diverse subset of the population without bias based on race, ethnicity, gender, or age (as determined by the protocol) until target numbers have been reached. Research recruitment flyers are also posted at the blood center. These flyers include a telephone number for donors to call if they are interested in learning about research participation.

Subjects who are recruited and eligible for WB donations in Cohort 1 will be automatically assigned to the FDP-CPD study arm. Similarly, plasmapheresis donors who are enrolled will automatically be assigned to the FDP-ACD study arm of Cohort 1. The same process for assigning subjects to the FDP-CPD and FDP-ACD arms in Cohort 2 will be applied.

For Cohort 3, which includes product crossover of FDP-ACD and FFP, only plasmapheresis donors who consent to the study are potentially eligible for study enrollment. Cohort 3 subjects are randomized no more than 48 hours prior to their first infusion in a 1:1 ratio to one of two treatment arms that will determine the order in which the two plasma treatment products, FFP and FDP-ACD, are to be infused across the two study infusion visits. Based on this, some subjects will receive FDP-ACD at the first infusion visit while others will receive FFP at the first infusion visit. Cohort 3 subjects who leave the study without completing both infusion visits will be replaced; the replacement subject, assigned a unique SID, will be assigned to the same treatment arm as the discontinued subject. The randomization list allows for over-enrollments and additional randomization slots to compensate for subjects who discontinue early. The Westat Statistician is responsible for the randomization assignments performed via the study website [https://www.fdpcollaboration.org]. Fifth floor HBC FDP research staff who randomize and prepare plasma products will complete the FDP-1 Randomization Worksheet, which contains a series of questions to verify subject eligibility. HBC FDP research staff will log on to the website and submit the worksheet information to request randomization. Shortly after the request is submitted, they will receive a confirmation email of the unmasked study arm assignment (including the randomization number). Fifth floor HBC FDP research staff will maintain records and prepare the appropriate plasma product according to the clinical site's SOPs and the study's MOP.

6.6.2. Blinding

This is a partial double-blind study. Blinding is not necessary for Cohorts 1 and 2 because they will only receive a single infusion of FDP. Cohort 3 subjects are to receive FDP at one infusion and the control product, FFP, at another. Cohort 3 subjects randomized to a treatment sequence are to remain blinded to the product they receive at each visit. Additionally, the PI, the RM, the PVG MD, and third floor HBC FDP research staff are blinded to the randomly assigned treatment sequence throughout the trial. FDP research staff, assigned to the fifth floor at HBC will be responsible for randomization, product preparation, and blinding. To ensure the product being used during infusion remains unknown to subjects, fifth floor HBC FDP research staff will

place a blinding bag over the infusion bag that will remain in place throughout the subjects' infusions.

Further efforts to achieve blinding will include the use of a limited list of clinical site personnel authorized to receive the unmasked randomization confirmation (only those who require this information to perform their duties).

6.6.3. Unblinding

Unblinding is not to occur until all study data are entered into the database, the data is cleaned, and the database is locked. Otherwise, unblinding of a subject's individual randomization code is only to be performed in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the investigational study product is essential for the clinical management or welfare of the subject. The reason for unblinding is to be clearly specified in the source documentation.

In the event of a medical emergency or serious medical condition, the PI should attempt to notify the sponsor prior to the request for emergency unblinding through 5th floor HBC FDP research staff. However, if the subject must be unblinded immediately, the PI will contact the study sponsor as soon as possible to report the unblinding.

Authority to request emergency unblinding is limited to the PI, RM, and the PVG MD. The PI will notify the Office of Regulated Activities, USAMMDA, Product Safety Surveillance Branch (PSSB) of the emergency unblinding as soon as possible. If an emergency unblinding occurs, the PSSB will immediately notify the DSMB Chair. The DSMB Chair will determine whether the DSMB members need to be involved immediately versus during the next DSMB meeting.

For the clinical site or the DSMB to request unblinding for a non-emergency situation, the following procedure must be followed for the site to receive approval to unblind the subject's treatment order assignment:

1. The PI will send the request to the US Army Medical Materiel Development Activity (USAMMDA), ORA, PSSB (usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil). The PSSB will notify the PVG MD and the un-blinded Westat Statistician of the request to un-blind. The request must include the subject's identification number, last completed study visit, date of last plasma infusion (or date of last donation visit if no infusion visit has taken place), and an explanation of why un-blinding information is requested (eg, subject has experienced a Grade 3 clinical toxicity that is related to the infusion);
2. If the PVG MD approves the request to un-blind, authorization will be sent to the un-blinded Westat statistician via email;
3. If the DSMB requires un-blinded data for Cohort 3, the DSMB Chair will send the request to the PSSB (usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil). PSSB will notify the Westat un-blinded biostatistician who will provide the un-blinded data directly to the DSMB for review.

6.7. Investigational Product

The investigational product, FDP, is manufactured at VSI, Minneapolis, MN, stored at 1°C -6°C prior to reconstitution, and shipped to the clinical site on an as-needed basis during the trial. One unit of FDP contains approximately 21.5 g of solids that consist of human plasma proteins and lipids. FDP will be reconstituted with 250 mL SWFI, USP.

Table 10 presents a summary description of the investigational product and comparator product.

Table 10: Investigational Product

Product Name	FDP	FFP
Dosage Form	Freeze dried human plasma prepared from FFP in a customized lyophilization bag and reconstituted with 250 mL SWFI, USP.	Plasma from WB or plasmapheresis collection, separated by centrifugation and frozen within 8 hours of collection.
Unit Dose	~270 mL	~270 mL
Route of Administration	IV infusion	IV infusion
Physical Description	Straw-colored cake that, upon reconstitution, looks similar in color and consistency to thawed FFP.	Liquid plasma separated from RBCs and frozen.
Manufacturer	VSI	Hoxworth Blood Center (FFP manufactured on site)
Lot Number	Donation Identification Number (DIN).	Same as the DIN; however, the suffix may change.
Product Indication	• Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors (eg, liver disease, disseminated intravascular coagulation (DIC)); • Patients undergoing massive transfusion who have clinically significant coagulation deficiencies; • Patients taking warfarin who are bleeding or need to undergo an invasive procedure before Vitamin K could reverse the warfarin effect or who need only transient reversal of warfarin effect; and	• Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors (eg, liver disease, DIC); • Patients undergoing massive transfusion who have clinically significant coagulation deficiencies; • Patients taking warfarin who are bleeding, or need to undergo an invasive procedure before Vitamin K could reverse the warfarin effect or who need only transient reversal of warfarin effect; • Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation

concentrates are available;

	• Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available.	• Transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP); and • Management of patients with rare specific plasma protein deficiencies, such as C1 inhibitor, when recombinant products are unavailable.
Contraindications	• To correct for coagulopathy in cases where a specific therapy would be more effective, such as Vitamin K, Cryoprecipitated Antihemophilic Factor (AHF), prothrombin complex concentrates used to reverse warfarin, or specific coagulation factor concentrates. • When blood volume can be safely and adequately replaced with other volume expanders.	• To correct for coagulopathy in cases where a specific therapy would be more effective, such as Vitamin K, Cryoprecipitated Antihemophilic Factor (AHF), prothrombin complex concentrates used to reverse warfarin, or specific coagulation factor concentrates. • When blood volume can be safely and adequately replaced with other volume expanders.

6.7.1. Investigational Product Packaging and Labeling

The RePlas™ FDP system consists of:

- One container of RePlas™ (~270 mL plasma equivalent), separately packaged within a foil pouch;
- One container of SWFI USP that contains 250 mL (B. Braun, NDA# N019633);
- A commercially available Fluid Transfer Set (B. Braun) for transfer of the SWFI fluid into the RePlas™ container; and
- A commercially available Blood Set (B. Braun), for infusion of the FDP to the subject.

The investigational product, RePlas™ FDP, is covered under an IND application. Each container will be labeled for human administration and will include the following statement: "Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use."

Each unit of manufactured FDP will be labeled with a unique DIN that is directly traceable to the original donor. The DIN will be carried throughout the study and recorded on the study case report forms (CRFs).

6.7.2. Investigational Product Storage and Preparation

FDP units will be shipped to the clinical site using the guidelines specified in the study-specific SOPs developed by VSI. The clinical site has developed a study-specific SOP to detail the process used for receiving and tracking FDP units from VSI.

Prior to reconstitution, FDP should be stored at 1°C to 6°C and the reconstitution fluid should be stored at room temperature (20°C to 24°C). Storage refrigerators and cabinets used for

investigational product should be in secure areas with controlled and limited access and clearly labelled as 'Active Product.' Temperatures should be monitored with a certified National Institute of Standards and Technology (NIST) thermometer or validated environmental monitoring system. Any temperature excursions must be reported to the sponsor's representative within 24 hours of knowledge of the excursion. Prior to infusion, FDP product must be reconstituted according to the procedures provided by the product manufacturer. Reconstituted FDP should not be frozen and should remain at room temperature until administration. Once reconstituted, transfusion with the FDP should begin within 4 hours. If transfusion has not started within 4 hours of reconstitution or the product is not used for other purposes, the unit cannot be used and must be identified as a quarantined unit, moved to quarantine, and then discarded.

FDP products that are damaged, experience temperatures outside of the defined parameters for product storage, and those that are unused are not to be infused unless written approval has been given by the sponsor's representative. Unused study product must be stored under appropriate conditions in a specified quarantine area separate from active product storage. At the direction of the sponsor's representative, FDP product units such as these must be discarded by the study site using their SOP, Discard of Blood Components (#CP-057-SOP).

6.7.3. Investigational Product Accountability

The sponsor's representative is responsible for distributing the investigational product to the *study site*. The sponsor's representative has delegated drug accountability responsibility for this product to *the PI;* however, the sponsor's representative has ultimate responsibility for product accountability. After the investigational product is distributed, the PI is responsible for and will maintain records of investigational product receipt, storage, reconstitution, accountability by subject, and investigational product remaining before final disposition. The PI may delegate, in writing, this responsibility to another individual, but the PI is ultimately responsible for the investigational product and its proper storage upon receipt at the study site until it is destroyed, as directed by the sponsor's representative.

The PI or designee must assure that the donor identity of the plasmapheresis products, and later downstream units of FFP or FDP manufactured from those products, is identical to the recipient of those products. Before infusion, the identity of the donor/recipient must be confirmed to agree with identity of the product label and ABO compatibility confirmed by testing using a minor cross-match and repeat typing of samples from the product.

All unused or partially used investigational product will be destroyed by the PI or designee by being incinerated and disposed of as biohazardous waste according to local SOPs, as directed by the sponsor's representative and as stipulated by local, state, and Federal regulations. Unused or partially used investigational product may only be destroyed or transferred after authorization has been received from the sponsor's representative.

Clinical monitors will confirm that procedures for the storage, dispensation, and return/destruction of investigational product are safe, adequate, and properly documented in accordance with the study protocol.

6.8. Duration of Subject Participation

Subjects in Cohort 1 will complete the study in approximately 3 months. Subjects in Cohort 2, Arm 3 will complete the study in approximately 4 months; subjects in Cohort 2, Arm 4 will require approximately 3 months. Subjects in Cohort 3 will complete the study in approximately 4 months. The first infusion for all cohorts is defined as Study Day 1. Study Day 15 is the second infusion for Cohort 3. The manufacturing time is currently estimated to be 5 weeks and although accounted for in study participation time, no subject activities are planned during this time. Screening and baseline assessment and informed consent visits will require approximately 2 hours. Final eligibility assessments and WB collection or plasmapheresis will require approximately 4 hours. On the day of infusion, the infusion and post-infusion studies will require approximately 8 hours.

For all cohorts, the on-site follow-up assessments will take 1 to 2 hours to complete, and the telephone assessments will take 15 to 20 minutes to complete. Cohorts 1 and 2 will have on-site follow-up assessments on Study Days 2, 8, and 29 and telephone follow-up assessments on Study Days 3, 4, and 15. Cohort 3 will have on-site follow-up assessments on Study Days 2, 8, 16, 22, and 43 and telephone follow-up assessments on Study Days 3, 4, 17, 18, and 29.

6.9. Dose-Adjustment Criteria

6.9.1. Safety Criteria for Dose Adjustment or Stopping Doses

If any of the following events occur, administration of investigational product will be discontinued until a thorough review of the events is undertaken by the PI, local Institutional Review Board (IRB) and/or the USAMRMC Office of Research Protections (ORP) Human Research Protection Office (HRPO), RM, and/or sponsor's safety office (USAMMDA, ORA, PSSB). The study may be resumed with the concurrence of the PVG MD, sponsor's representative, PI, and the FDA.

The following SRs will be applied to all study subjects throughout the trial:

1. An SAE that is determined to be possibly, probably, or definitely related to the study product;
2. An AE related to the study product that the PI, RM, and/or the sponsor's PVG MD agree jeopardizes the subject's health or safety;
3. An AE related to the study product that requires medical or surgical intervention to prevent occurrence of an SAE;
4. A post-infusion, abnormal coagulation function assay which is also a greater than 20% change from baseline for PT/INR and/or aPTT values (eg, a subject who has a baseline INR of 1.0 with a post-infusion INR of 1.3 will activate an SR, because this is an abnormal coagulation function assay result that is also a greater than 20% change from the pre-infusion assay result); and/or
5. Post-infusion development of hemolysis or DVT, cardiac ischemia, or PE. DVT will be determined following the ICSI Health Care Guideline: Venous Thromboembolism Diagnosis and Treatment (includes assessment of D-Dimer results and Wells criteria ≥ 2). (Dupras et al-2013)

If any of the above conditions occur, the study will be paused to assess continuation of the study. A form (Appendix C) will document the decisions made by the PI, RM, and/or PVG MD regarding the review of the data from the first 5 subjects in each cohort. The completed form will be emailed to the clinical site, Westat, and USAMRMC USAMMDA ORA and will be maintained as part of the study documentation.

6.10. Trial Treatment Randomization Codes

The data management center for the study will provide a list of the randomized order for administration of FDP and FFP for Cohort 3. Unblinding prior to the end of the study will occur only to protect subject safety.

The codes will be maintained by the website randomization system. The system will only send out website randomization confirmation with unmasked treatment assignment to the personnel that have been designated in the randomization, masking, and unmasking plan. Unblinding will occur at the end of the study after all study data are entered in the database, cleaned, and the database is locked. Study arm assignment information will only be provided to 5th floor HBC FDP research staff.

6.11. Identification of Data to be Recorded on the Case Report Forms

The electronic case report form (eCRF) data will be transcribed from source documentation. No source data will be recorded directly on the eCRF (i.e., without prior written or electronic record of data). The transcribed data will be consistent with the source documents or the discrepancies will be explained.

For more information on data handling, refer section 15.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Recruitment of Subjects

HBC maintains lists of potential study subjects who have previously donated WB or plasma at the site and have indicated an interest in participating in research studies. Site personnel will contact (Appendix D) those people who have indicated an interest in research participation to inform them about this study. If the potential subject expresses an interest in learning more about the study and/or participating, then a screening visit will be scheduled. In addition to this process, advertisements (Appendix E) for healthy volunteers may also be used to recruit subjects. The subjects are typically not socioeconomically disadvantaged.

Subjects will be screened for inclusion as they present to the clinical site with an interest in participating and provide written informed consent. Subjects will be selected based on inclusion/exclusion criteria and eligibility requirements as specified in the study protocol, without any limitations to gender or ethnicity.

Recruitment of Cohort 2 subjects will begin following the infusion of the last subject in Cohort 1. Enrollment, screening, and collection visits will be completed but infusion visits will not occur until the DSMB recommends and the Sponsor provides their approval to proceed. The same process will also be applied to the recruitment for Cohort 3 subjects. Concurrent infusions will

not take place across cohorts ensuring infusions at the next higher does do not begin until all subject infusions at the previous dose have been completed.

Refer to section 5.9 for a detailed description of the subject population.

7.2. Eligibility Screening

Subjects who meet all the inclusion criteria and sign the informed consent form (ICF), will be enrolled in the study via the Oracle© Clinical (OC) Remote Data Capture (RDC) database. Each subject will be identified by a sequential number starting with 1. Demographic data (age, gender, and race/ethnicity) will be collected. Each subject must meet all inclusion and no exclusion criteria. In addition to the inclusion/exclusion criteria, the subject must also be eligible for donation based on the AABB donor history questionnaire (with exceptions for travel deferral). The PI or designee will make the final decision regarding eligibility. Only subjects deemed eligible based on all required screening activities will be enrolled. To determine and confirm subject eligibility for enrollment, subjects are required to:

- Provide a complete medical history, including concomitant medications;
- Undergo a complete physical examination that includes measurement of height, body weight, and vital signs (blood pressure, heart rate, respiration rate, and temperature), and evaluation of cardiopulmonary systems, basic neurological function, and presence of DVT or PE. DVT will be assessed in conjunction with a subjects' D-dimer test results and Wells scale score, similar to the ICSI DVT Diagnosis Algorithm (Dupras et al-2013);
- Provide a urine sample for a toxicology drug screen, urinalysis for occult organ dysfunction and measurement of specific gravity, pH, glucose, ketones, protein, blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen. Pregnancy tests will be performed for all females; and
- Provide blood samples for all tests as indicated in the Schedule of Events tables (Table 4, Table 5, Table 6, and Table 8).

7.3. Re-Screening Visits

To ensure ongoing subject eligibility, subjects will be rescreened if the interval between screening and infusion exceeds 12 weeks, providing adequate time to identify changes in clinical and laboratory values that would impact subjects' eligibility. The same tests and procedures described in section 7.2 will be repeated during this visit.

7.4. Subject Inclusion Criteria

Subjects must meet all of the following criteria to be included in the study:

- Males and non-pregnant/non-breastfeeding females;
- For females, a minimum weight of 140 pounds and maximum weight of 220 pounds; for males a minimum weight of 140 pounds and a maximum weight of 250 pounds;
- Ages 18-55 years;
- Subject self-reports that he or she feels well and healthy;

- Subject scores ≥ 35 on the Duke Activity Status Index (Appendix F);
- Subject is able to donate a unit of WB or plasma by plasmapheresis based on the AABB donor history questionnaire with modifications indicated: subjects with history of travel which puts them at risk for Creutzfeldt-Jakob Disease, malaria, or Zika will be eligible to participate;
- Has read the educational materials on donating blood and has had his or her questions answered;
- Able and willing to provide written informed consent;
- Available for the duration of the trial, which is approximately 12 weeks for subjects in Cohort 1 and Cohort 2, Arm 4; approximately 16 weeks for Cohort 2, Arm 3 and Cohort 3 (includes time for collections, product manufacture, and infusions), and able to come to the treatment clinic for scheduled study visits;
- Females of childbearing potential should either be surgically sterile (hysterectomy or tubal ligation), or should use a highly effective medically accepted contraceptive regimen. Highly effective methods of birth control are defined as those which result in a lower failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, condoms with spermicide, or vasectomized partner;
- All females must have a negative urine pregnancy test prior to enrollment; and
- Understands the English language.

7.5. Subject Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

- Known liver, kidney, cardiovascular, neurologic, gastrointestinal, blood, endocrine/metabolic, autoimmune or pulmonary disease, or treated or untreated hypertension;
- Cancer of any kind, under treatment or resolved;
- Known or past coagulopathy conditions;
- Any conditions, medications, etc. on the AABB medical deferral list;
- Past history of asthma (defined as use of a prescribed daily asthma controller medication or required asthma medication in the past 2 weeks);
- Past diagnosis of stroke, DVT, venous or arterial thrombosis, blood clots, or transient ischemic attack;
- Family history of venous or arterial thrombosis before the age of 50 in first degree relatives (i.e., biological parents, full siblings, or children);
- D-dimer test result ≥ 0.5 FEU/mL;
- History of an abnormal Electrocardiogram (EKG);

- Current smoker (defined as having smoked within the last 6 months);
- Known HIV or Acquired Immunodeficiency Syndrome (AIDS)-related illness or received a positive test result for HIV infection;
- Positive test for HBV, HCV, or HTLV;
- History of significant treated or untreated mental health issues;
- Female subject who is pregnant, lactating, or with a positive pregnancy test;
- Currently taking an antibiotic or another medication for an infection;
- Treatment or use of aspirin (or other platelet inhibiting agents) within 14 days of study donation and infusion visits;
- Currently using any medications for anticoagulant therapy;
- Previous use of clotting factor concentrate(s);
- Receipt of blood or blood products within the past 12 months;
- In the past week, has had a headache and fever at the same time;
- Known intolerance to any excipients (citrate) in the study drug formulation;
- Systolic blood pressure greater than 140 mmHg;
- Diastolic blood pressure greater than 90 mmHg;
- Temperature greater than 100°F;
- Known hematocrit less than 38% for both male and female donors;
- Positive DAT;
- Treatment with any investigational agent within 1 month before treatment infusion for this trial;
- Participation in any phase of any other investigational trials while participating in this trial;
- Unwilling or unable to comply with the requirements of this protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's return for follow-up visits on schedule;
- Other unspecified reasons that, in the opinion of the PI, make the subject unsuitable for enrollment; or
- Institutionalized because of legal or regulatory order.

7.6. Subject Withdrawal Criteria

Each subject may withdraw consent at any time during the study without penalty. Counseling about the subject's health will be provided if he or she decides to discontinue participation in the study. Medical advice regarding what is in the best interest of the subject will be provided.

The PI may discontinue the subject's activity without the subject's consent if any of these criteria are met:

- A subject fails to comply with study procedures;
- A subject's safety or health may be compromised by further participation; or
- A subject's Primary Care Physician wishes to withdraw the subject.

7.6.1. When and How to Withdraw Subjects

A subject may end his or her participation in the study at any time. If a subject withdraws, the PI will make a reasonable effort to determine the reason for the withdrawal from the study and to complete termination procedures as described in section 8.4. Telephone calls, registered letters, and email correspondence are considered reasonable effort. A minimum of 2 documented attempts to contact the subject should be made over the course of 1 week. If the site personnel receive no response, they should send a registered letter requesting that the subject contact the site regarding his or her status in the study. If the subject does not respond at this point, the date the certified letter was mailed will be considered the date of study withdrawal. For subjects leaving the study, a targeted examination may be performed, if medically indicated and if permitted by the subject.

A subject may be withdrawn for an AE or SAE resulting in a safety concern or for noncompliance with protocol requirements. When a subject withdraws due to an AE or is withdrawn by the PI due to an AE, the PVG MD, the sponsor's safety office (USAMRMC USAMMDA ORA) must be notified within 72 hours (usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil). The PI must follow specific policies regarding the timely reporting of AEs and SAEs to the local IRB (section 10.6.2). In all cases, the PI will make a reasonable effort to complete study termination procedures.

If a subject meets the withdrawal conditions for a concomitant medication violation or noncompliance, this should clearly be stated in the source document and the study termination eCRF.

7.6.2. Data Collected for Withdrawn Subjects

If a subject is withdrawn, all data collected up to the time of withdrawal will be reported. Ongoing AEs should be followed to resolution or stabilization, if the subject consents to passive review of his or her medical record. The study termination eCRF will be completed, with the reason for withdrawal specified.

7.6.3. Replacement of Subjects

A total of 24 subjects (8 in each cohort) are to fully complete the trial. Depending on the cohort, study completion is defined as:

- Cohorts 1 and 2: infused with autologous FDP and completion of the 7-day post-infusion follow-up visit; and
- Cohort 3: infused with both the autologous experimental and control products per the assigned treatment sequence and completion of the 7-day post-infusion follow-up visit subsequent to the second infusion.

In cases where subjects discontinue participation prior to study completion, a replacement subject will be enrolled in the study. The replacement, assigned a new and unique SID, will be assigned to the same treatment arm as the discontinued subject. This is necessary to maintain the 1:1 subject ratio across study arms.

7.6.4. Follow-Up for Withdrawn Subjects

Subjects who are withdrawn from the study will be followed to satisfactory resolution of any ongoing AEs (or until the PI deems the event to be chronic/stable) at the time of withdrawal by passive observation and recording of the subject's medical record, if the subject consents to this process.

8. TREATMENT OF SUBJECTS

8.1. Whole Blood and Plasma Collection

The purposeful use of plasmapheresis in this study, particularly for Cohort 3 subjects, provides practical advantages to subjects (eg, fewer required collection visits) and minimizes potential issues related to subject safety. WB donations generally provide a net volume of approximately 250 mL of derived plasma and typically require a 56-day interval between donations. In this study, subjects who are required to make more than one autologous WB donation (eg, subjects in Cohort 2, Arm 3), the donation interval will be abbreviated to 28 days. Plasmapheresis collections, in contrast, have a much shorter 7- to 10- day donation interval since there is minimal loss of red blood cells (RBCs) during the process. The volume that can be collected during single plasmapheresis is ≤ 800 mL, depending on the donor's size, which is over twice the plasma volume derived from WB donation. Limiting enrollment of subjects to those who weigh ≥140 lbs and ≤ 220 lbs will help ensure each autologous plasmapheresis yields 600 mL to 800 mL plasma based on established volume limits for automated plasma collection (FDA-1992). Regardless of cohort or treatment arm, all subjects will have SPEP performed at each plasmapheresis collection. If any abnormalities are detected, subjects will be referred to a physician, scheduled for early withdrawal, and replaced with another subject. For subjects undergoing multiple plasmapheresis collections, total protein will be performed STAT or up to 24 hours prior to initiating the plasmapheresis. Total protein will only be performed at subsequent plasmapheresis sessions, not during the first collection. All subjects regardless of cohort or treatment arm will be provided with information and instructions regarding the use of iron supplements (see Appendix G) during the donation period.

Following standard blood product SOPs, subjects' plasma products collected, manufactured, and prepared for autologous infusion will be visually examined. The visual inspection of both FFP and reconstituted FDP will include observation for signs of lipemia, hemolysis, clotting, and macroscopic particulate matter. Plasma units that do not meet the visual examination criteria will be discarded per the site's SOP for the destruction of blood and blood products.

8.1.1. Cohort 1 Blood and Plasma Collection

WB donors who are enrolled in the study will automatically be assigned to the FDP-CPD study arm of Cohort 1. Similarly, plasmapheresis donors who are enrolled will automatically be assigned to the FDP-ACD study arm of Cohort 1. Subjects in Treatment Arm 1 will receive a 1

unit (approximately 270 mL) transfusion of FDP manufactured from WB-derived plasma. Subjects in Treatment Arm 2 will receive a 1 unit (approximately 270 mL) transfusion of FDP manufactured from plasmapheresis. During the collection visit all subjects in Cohort 1will:

- Be asked to provide information about medical history, concomitant medications, and AEs since the screening visit;
- Undergo an abbreviated physical exam which includes vital signs (blood pressure, heart rate, respiration rate, and temperature) and a general assessment of health;
- Complete the AABB Donor History Questionnaire; and
- Provide a sample of blood for hematocrit testing prior to donation per the SOPs in place at the site.

Treatment Arm 1 subjects will provide a single unit (approximately 500 mL) WB donation using the standard WB donation procedures in place at the site. Post-donation, subjects will be monitored for any adverse effects associated with WB donation (see section 5.6.1.2).

Treatment Arm 2 subjects will provide a single unit plasmapheresis donation (approximately 600 mL) using the standard plasmapheresis donation procedures in place at the site. Post-donation, subjects will be monitored for any adverse effects associated with plasmapheresis donation (see section 5.6.1.3).

If a subject has low hematocrit on the day of donation, they may, at the discretion of the investigator, be rescheduled for a second attempt at blood/plasma collection.

Subjects who provide low volume donations, <450 mL for Treatment Arm 1 and <500 mL for Treatment Arm 2, may, at the discretion of the investigator, be withdrawn from the study or rescheduled for a second attempt at blood/plasma collection. If, for example, the low volume donation occurs in a subject who enrolled early enough for a second donation attempt to be made within the scheduled time frame for the cohort, the subject will remain in the study and be given the opportunity for a second donation. Those subjects in Treatment Arm 2 who provide a low volume donation and who are scheduled for another attempt at the plasmapheresis collection will have another SPEP performed in addition to STAT total protein. All low-volume collections will be discarded by the clinical site following their SOP for handling blood and blood products.

8.1.2. Cohort 2 Blood and Plasma Collection

Cohort 2 subjects will be assigned to 1 of the 2 treatment arms as described in section 6.6.1. Subjects in Treatment Arm 3 will receive a 2 unit (approximately 540 mL) transfusion of FDP manufactured from WB-derived plasma. Subjects in Treatment Arm 4 will receive a 2 unit (approximately 540 mL) transfusion of FDP manufactured from plasmapheresis. During collection visits all Cohort 2 subjects will:

- Be asked to provide information about medical history, concomitant medications, and AEs since the screening visit;
- Undergo an abbreviated physical exam which includes vital signs (blood pressure, heart rate, respiration rate, and temperature) and a general assessment of health;
- Complete the AABB Donor History Questionnaire; and

- Provide a sample of blood for hematocrit testing prior to (each) donation per the SOPs in place at the site.

Treatment Arm 3 subjects will provide a single unit (approximately 500 mL) WB donation using the standard WB donation procedures in place at the site. Post-donation, subjects will be monitored for any adverse effects associated with WB donation (see section 5.6.1.2). Due to the volume of plasma required to manufacture 2 units (approximately 540 mL, total) of FDP, Treatment Arm 3 subjects will be scheduled for a second WB donation session, no less than 28 days from the date of their first donation. Subjects in this arm who provide a low-volume donation (< 450 mL) may, at the discretion of the investigator, be withdrawn from the study or scheduled for a second donation attempt. The donation portion of each WB donation visit is expected to take no more than 1 hour. The procedures described above will be followed at both WB donation visits.

Treatment Arm 4 subjects will provide a single unit plasmapheresis donation (up to 800 mL) using the standard procedures in place at the site. Subjects will undergo SPEP, which will be measured during their plasmapheresis donation. Post-donation, subjects will be monitored for any adverse effects associated with plasmapheresis donation (see section 5.6.1.3). A second plasmapheresis donation visit should not be required for Treatment Arm 4 subjects. Subjects providing a low volume plasmapheresis donation (< 500 mL) may, at the discretion of the investigator, be withdrawn from the study or scheduled for a second donation attempt. If a subsequent visit is scheduled to collect the volume of plasma required to manufacture the 2 units (approximately 540 mL, total) of FDP, an additional visit may be scheduled no less than 7 days from the date of the first donation. SPEP and STAT Total Protein will both be performed at any subsequent collection visits as a condition of initiating plasmapheresis.

Following standard blood collection SOPs, subjects who present to a collection visit with a low hematocrit may, at the discretion of the PI, be rescheduled for a later blood/plasma collection.

All low-volume collections will be discarded by the clinical site following their SOP for handling blood and blood products.

8.1.3. Cohort 3 Plasma Collection

WB-derived plasma will not be used in Cohort 3 due to safety concerns regarding the number of donations required to collect the volume of plasma needed to manufacture 3 units (approximately 810 mL) of FDP and 3 units (approximately 810 mL) of FFP. All subjects in Cohort 3 will undergo plasmapheresis collection. Cohort 3 subjects will be randomized no more than 48 hours prior to the first infusion to 1 of 2 treatment arms that will be based on the order of the products received. Subjects in Treatment Arm 5 will receive a 3 unit (approximately 810 mL) transfusion of FDP followed by a 3 unit (approximately 810 mL) transfusion of FFP. Subjects in Treatment Arm 6 will receive a 3 unit (approximately 810 mL) transfusion of FFP followed by a 3 unit (approximately 810 mL) transfusion of FDP. Subjects will be blinded to their treatment order assignments.

During the Collection Visits, all Cohort 3 subjects will:

- Be asked to provide information about medical history, concomitant medications, and AEs since the screening visit;

- Undergo an abbreviated physical exam which includes vital signs (blood pressure, heart rate, respiration rate, and temperature) and a general assessment of health;
- Complete the AABB Donor History Questionnaire;
- Provide a sample of blood for hematocrit testing prior to (each) donation per the SOPs in place at the site; and
- Provide a plasma donation by plasmapheresis in compliance with the clinical site's SOPs regarding plasmapheresis donation.

Cohort 3 subjects will need to make 2 to 3 plasmapheresis donations (up to 800 mL per collection) that will be scheduled to take place, minimally, a week apart. Post-donation, subjects will be monitored for any adverse effects associated with plasmapheresis donation (see section 5.6.1.3). The SPEP will be routinely performed at as part of all Cohort 3 collection visits. Should the SPEP results reveal the subject as ineligible for their current plasmapheresis, the subject may be rescheduled to return in no less than 7 days. Just prior to Cohort 3 subjects' second or subsequent plasmapheresis donation at each plasmapheresis collection, a SPEP test will be performed. After the first plasmapheresis collection, a STAT Total Protein will be performed as a condition of initiating plasmapheresis at subsequent collection visits. Post-donation, all subjects will be monitored for any adverse effects associated with plasmapheresis donation (see section 5.6.1.3).

Approximately 10% of plasma units that are supplied for manufacturing of FDP are damaged during the process. Those units must be discarded and cannot be infused. If that happens to a subject's plasma unit, they will be asked to return to the clinic for additional plasmapheresis collections in order to meet the total required volume for the manufacturing of 1,620 mL of plasma.

Subjects who do not meet the study's minimum collection volume requirements of 500 mL during plasmapheresis may be withdrawn from the study. The low volume donation collections (< 500 mL) will be discarded per the clinical site's SOP for handling blood and blood products.

8.2. Plasma Infusion

8.2.1. Cohorts 1 and 2 Plasma Infusion

Prior to plasma infusion of subjects' in Cohorts 1 and 2, the following activities and procedures must be completed:

- Review of medical history, concomitant medications, and AEs since the collection visit(s);
- Conduct a complete physical examination that includes measurement of, body weight, and vital signs (blood pressure, heart rate, respiration rate, and temperature), and evaluation of cardiopulmonary systems, basic neurological function, and presence of DVT, cardiac ischemia, or PE. DVT will be assessed in conjunction with a subjects' D-Dimer test results and Wells scale score.(Dupras et al-2013);
- Collect urine and blood samples as noted for all tests listed in the Schedule of Events tables (Table 4, Table 5, and Table 6);

- Cross-match subject's RBCs to FDP; and
- Reverse ABO type on FDP.

At the discretion of the PI, a study plasma infusion may not be given if, in the PI's opinion, the subject's clinical status precludes a study plasma infusion and the planned protocol assessments. The reason for the PI's decision to withhold a study plasma infusion will be documented in the source documents and eCRFs. This does not preclude a standard of care plasma infusion.

After reconstitution of the FDP, a visual examination for signs of lipemia, hemolysis, clotting, or other issues that impact the quality and acceptability of the plasma for re-infusion will be performed. This visual inspection of FDP also includes observation of macroscopic particulate matter. Reconstituted FDP that does not meet visual examination criteria will be discarded per the site's SOP for the destruction of blood and blood products.

The date, start, and stop times of each plasma infusion will be recorded in the source document and eCRF. The scheduled dose of FDP will be transfused into subjects using a standard plasma administration set according to the clinical site's SOPs. The plasma product will be pumped into the vein at an initial rate of approximately 2-3 mL/minute for the first 10 minutes, and then the rate will be adjusted to not more than 10 mL/minute until completion of the plasma infusion. During the course of the infusion, vital signs (blood pressure, heart rate, respiration rate, and temperature) for all subjects will be monitored every 15 minutes (± 5 minutes) until the transfusion is completed.

Subjects will be observed during and after the study plasma infusion for evidence of acute transfusion reactions including: allergic reactions, bradycardia, tachycardia, or other cardiac dysrhythmia, hypertension, hypotension, dyspnea, hemolysis, fever, chills, thromboembolic events, bleeding, and infection. Subjects will remain at the study site under direct observation and actively monitored for a minimum of 5 to 6 hours post-infusion.

Vitals will be measured every 30 minutes (± 5 minutes) up to 4 hours post-infusion and then once every 4 hours (± 40 minutes) until the subject is released. The following laboratory tests will be performed at 30 minutes (± 5 minutes) and at 4 hours (± 40 minutes) post-infusion (see Table 7):

- Urinalysis;
- CBC (Hematocrit, Hemoglobin, Platelet Count, RBC Count, WBC Count);
- Chemistry panel (pH, Ionized Calcium and Total Magnesium [at 30 minutes post-infusion only], ALP, ALT, AST, Calcium, bicarbonate, lactate, Chloride, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, BUN, and Creatinine);
- PT/INR and aPTT; and
- D-dimer testing.

Prior to release, subjects will undergo an additional physical evaluation (eg, focus on cardiopulmonary systems, basic neurological function, and presence of DVT). The investigator will interpret exam findings in conjunction with the subjects' 4-hour post-infusion D-dimer test results and Wells criteria to determine the medical suitability for release.

8.2.2. Cohort 3 Plasma Infusion

Cohort 3 subjects will be scheduled for 2 infusion visits to occur on Study Days 1 and 15. Because of the crossover, no more than 48 hours prior to administration of a subject's first infusion, he or she will be randomly assigned to a study arm (Arm 5 or Arm 6) indicating the specific product to be administered. The alternate product of what is received at the first Infusion Visit, either FDP (Test) or FFP (Control), will be infused at the second Infusion Visit.

At the time of each scheduled Infusion Visit, the prior activities and procedures must be completed for each subject before infusion may begin:

- Review of medical history, concomitant medications, and AEs since the collection visit(s);
- Conduct a complete physical examination that includes measurement of weight, and vital signs (blood pressure, heart rate, respiration rate, and temperature), and evaluation of cardiopulmonary systems, basic neurological function, and presence of DVT, cardiac ischemia, or PE. DVT will be assessed in conjunction with a subjects' D-dimer test results and Wells scale score (Dupras et al-2013).
- Collect urine and blood samples as noted for all tests listed in the Schedule of Events table (Table 8);
- Cross-match subject's RBCs to FDP or FFP; and
- Reverse ABO type on FDP or FFP.

At the discretion of the PI, a study plasma infusion may not be given if, in the PI's opinion, the subject's clinical status precludes a study plasma infusion and the planned protocol assessments. The reason for the PI's decision to withhold a study plasma infusion will be documented in the source documents and eCRFs. This does not preclude a standard of care plasma infusion.

After reconstitution of the FDP or FFP, a visual examination for signs of lipemia, hemolysis, clotting, or other issues that impact the quality and acceptability of the plasma for re-infusion will be performed. This visual inspection of reconstituted FDP also includes observation of macroscopic particulate matter. Reconstituted FDP or FFP that does not meet visual examination criteria will be discarded per the site's SOP for the destruction of blood and blood products.

The date, start, and stop times of each plasma infusion will be recorded in the source document and eCRF. The scheduled dose of FDP or FFP will be transfused into subjects using a standard plasma administration set according to the clinical site's SOPs. The plasma product will be pumped into the vein at an initial rate of approximately 2-3 mL/minute for the first 10 minutes, and then the rate will be adjusted to not more than 10 mL/minute until completion of the plasma infusion. During the course of the infusion, vital signs (blood pressure, heart rate, respiration rate, and temperature) for all subjects will be monitored every 15 minutes (± 5 minutes) until the infusion is completed.

Subjects will remain at the study site and be actively monitored under direct observation for a minimum of 5 to 6 hours post-infusion. They will be asked about and observed during and after the study plasma infusion for evidence of acute transfusion reactions including: allergic reactions, bradycardia, tachycardia, or other cardiac dysrhythmia, hypertension, hypotension, dyspnea, hemolysis, fever, chills, thromboembolic events, bleeding, and infection.

Vitals will be measured every 30 minutes (± 5 minutes) up to 4 hours post-infusion. Measurement of vitals will then be decreased to every 4 hours (± 40 minutes) until the subject is released. The following laboratory tests will be performed at 30 minutes (± 5 minutes) and at 4 hours (± 40 minutes) post-infusion (see Table 9):

- Urinalysis;
- CBC (Hematocrit, Hemoglobin, Platelet Count, RBC Count, WBC Count);
- Chemistry panel (pH, Ionized Calcium and Total Magnesium [at 30 minutest post-infusion only], ALP, ALT, AST, Calcium, Bicarbonate, lactate, Chloride, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, BUN, and Creatinine);
- PT/INR and aPTT;
- DAT (IgG and C3);
- Coagulation factor tests (Factors I, II, V, VII, VIII, IX, X, XI, D-Dimer, von Willebrand Factor activity, Protein C activity, and Protein S activity); and
- PF 1+2, TAT, AT-III, Alpha-2 Antiplasmin, and C3a des Arg at 30 minutes post-infusion only. These tests are for research purposes only and will not be used to assess subject safety.

Prior to release, subjects will undergo an additional physical evaluation (eg, focus on cardiopulmonary systems, basic neurological function, and presence of DVT). The investigator will interpret exam findings in conjunction with the subjects' 4-hour post-infusion D-dimer test results and Wells criteria to determine the medical suitability for release.

8.3. Follow-Up Visits

8.3.1. 24-Hour Follow-Up Visit

Subjects in all 3 cohorts should be scheduled for an on-site follow-up visit 24 hours (± 3 hours) after the completion of the plasma infusion. During this visit, the following procedures will be performed:

- Review of medical history, concomitant medications, and AEs since the infusion visit;
- Conduct a complete physical examination that includes measurement of, body weight, and vital signs (blood pressure, heart rate, respiration rate, and temperature), and evaluation of cardiopulmonary systems, basic neurological function, and presence of DVT, cardiac ischemia, or PE. DVT will be assessed in conjunction with a subjects' D-Dimer test results and Wells scale score; and
- Collect urine and blood samples as noted for all tests listed in the Schedule of Events tables (Table 4, Table 5, Table 6, and Table 8).

NOTE: Since subjects in Cohort 3 receive 2 separate infusions, a 24-hour post-infusion follow-up visit will be scheduled after each infusion.

8.3.2. Telephone Follow-Up

In addition to scheduled on-site follow-up visits, subjects in all 3 cohorts will be contacted by phone at 48 hours (± 2 hours), 72 hours (± 2 hours), and 14 days (± 2 hours) (ie, Study Days 3, 4, and 15) after the completion of the plasma infusion. During the calls, subjects will be asked specific questions (Appendix H) regarding possible signs and symptoms of any AEs they may have experienced and any concomitant medications taken since the infusion visit. The date and time of the call, as well as the subject's responses will be recorded in the source documents and the eCRF.

Cohort 3 subjects' will have no 14- day follow-up phone call after the first infusion since it would occur on the same day as the second infusion (Study Day 15). The 14-day follow-up phone call subsequent to the second infusion visit will occur on Study Day 29.

8.3.3. 7-Day Follow-Up Visit

A post-infusion follow-up visit will be scheduled 7 days (± 1 day) post-infusion for subjects in all 3 cohorts. The following procedures will be performed at these visits:

- Review of medical history, concomitant medications, and AEs since the last telephone follow-up contact;
- Abbreviated physical exam which includes vital signs (blood pressure, heart rate, respiration rate, and temperature) and a general assessment of health; and
- Collect blood samples as noted for all tests listed in the Schedule of Events tables (Table 4, Table 5, Table 6, and Table 8).

NOTE: Since subjects in Cohort 3 receive 2 separate infusions, a 7-day post-infusion follow-up visit should also be scheduled after the second infusion. The second 7-day post-infusion follow-up visit will also follow the procedures described in this section.

8.3.4. 28-Day Follow-Up Visit

A post-infusion follow-up visit will be scheduled 28 days (± 1 day) post-infusion for subjects enrolled in Cohorts 1 and 2. For subjects enrolled in Cohort 3, a 28-day post-infusion follow-up visit will take place after the second plasma infusion, only, approximately 42 days after the first infusion visit. The following procedures will be performed at these follow-up visits:

- Review of medical history, concomitant medications, and AEs since the 14-day telephone follow-up contact;
- Abbreviated physical exam which includes vital signs (blood pressure, heart rate, respiration rate, and temperature) and a general assessment of health;
- Collect blood samples as noted for all tests listed in the Schedule of Events tables (Table 4, Table 5, Table 6, and Table 8); and
- Exit interview concluding the subject's study participation.

8.3.5. Biological Samples

Samples collected under this protocol will be used to conduct protocol-related safety and efficacy evaluations as noted in Table 4, Table 5, Table 6, and Table 8. No genetic testing will be performed on these samples. Total volumes, by visit, for laboratory tests performed during the course of the study are listed in Table 7 and Table 9.

Samples will be stored in a quality-controlled environment. Transport and storage of these biological samples will be handled according to the clinical site's SOP. Any study for the future use of these biological samples will have IRB approval. In addition, a subject may decide at any point to withdraw consent for the future use of his or her samples. Should a subject withdraw consent for the use of his or her samples, the samples will be destroyed according to the clinical site's SOP.

8.4. Early Withdrawal Procedures

Subjects who withdraw from the study at any time before the Infusion Visit who have not experienced an AE will have the Exit Interview administered by telephone. Subjects who withdraw from the study any time after the infusion and before the 7-Day Post-Infusion Follow-Up Visit will be asked to complete all Early Discontinuation Visit procedures to ensure safety and to collect as much data as possible:

- Review of medical history, concomitant medications, and AEs since the telephone follow-up contact;
- Abbreviated physical exam which includes vital signs (blood pressure, heart rate, respiration rate, and temperature) and a general assessment of health; and
- Laboratory tests including:
  - Urinalysis;
  - Urine pregnancy test (females only);
  - CBC (Hematocrit, Hemoglobin, Platelet Count, RBC Count, WBC Count);
  - Chemistry panel (ALP, ALT, AST, Calcium, Chloride, Potassium, Sodium, Lactate, Bicarbonate, Glucose, Total Bilirubin, Total Protein, BUN, and Creatinine);
  - PT/INR and aPTT;
  - DAT;
  - D-dimer; and
  - COHORT 3 ONLY – Coagulation factor tests (Factors I, II, V, VII, VIII, IX, X, XI, von Willebrand factor, Protein C activity, and Protein S activity), PF 1+2, TAT, AT-III, alpha-2 antiplasmin, and C3a des Arg. PF 1+2, TAT, AT-III, alpha-2 antiplasmin, and C3a des Arg are for research purposes only and will not be used to assess subject safety.

8.5. Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- To perform confirmatory laboratory testing for clinically abnormal values; and
- If the PI feels that it is clinically required for safety reasons related to the subject's participation in the study.

Findings during these unscheduled visits must be reported on the eCRF in the Unscheduled Visit section.

8.6. Concomitant Medications

Subjects should not be taking prescription medications or over the counter drugs included in the list of exclusion criteria or on the eligibility assessment questionnaire while participating in this study. If the subject develops a medical condition between the time of plasmapheresis and re-infusion, the medication should be approved by the PI prior to the subject taking the medication. If a medication is taken that is contraindicated to the objectives of the study, the infusion will either be deferred or the subject will be taken off study.

The AABB Medication Deferral List includes:

- Proscar© (finasteride);
- Avodart©, Jalyn (dutasteride);
- Propecia© (finasteride);
- Accutane© (Amnesteem, Claravis, Sotret, isotretinoin);
- Soriatane© (acitretin);
- Tegison© (etretinate);
- Growth hormone from human pituitary glands;
- Insulin from cows (bovine, or beef insulin);
- Hepatitis B immune globulin;
- Plavix (clopidogrel) and Ticlid (ticlopidine);
- Feldene; and
- Experimental medication or unlicensed (experimental) vaccine.

8.7. Procedures for Monitoring Subject Compliance

A record of each study plasma infusion will be documented in the clinical database via relevant eCRFs and additional source documentation. Only the individual product unit identifier will be stored in the clinical database. The clinical database will document that the infusion occurred. Additionally, for unit identifiers documented in the clinical database, final disposition will be reconciled by linking to a separate Plasma Unit Tracking Form that will be maintained by 5th floor HBC FDP research staff and VSI.

9. PHARMACOKINETIC ASSESSMENTS

No pharmacokinetic assessments will be done in this study.

10. SAFETY ASSESSMENT

Safety monitoring throughout the study will identify safety issues and concerns. The process of continual review of the data and the imperative to appropriately and promptly address identified safety concerns is a shared effort of the PI and clinic staff, the designated clinical and research monitors, USAMRMC USAMMDA ORA, and the PVG MD for the protocol. A DSMB will be convened for this protocol. The roles and responsibilities of the monitors and DSMB are outlined below.

Clinical Site: Consists of the PI, RM, Clinical Research Coordinator, and other research staff. The clinical site is responsible for ensuring the safety of study subjects by managing, collecting, and recording AEs/SAEs, and reporting SAEs appropriately according to the requirements of the protocol and their local IRB. The PI will promptly forward all SAEs to the IRB and HRPO.

Research Monitor: The Department of Defense research monitor is responsible for overseeing the safety of the research and reporting observations/findings to the IRB or a designated institutional official. The research monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide independent reports of the events to the IRB. The research monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

In addition to the responsibilities above, the research monitor is required to review and provide unbiased written reports for all SAEs and subject deaths to the USAMMDDA PSSB (Safety Office) within 24 hours of becoming aware of the event. The report provided must include at a minimum, a brief summary of the research monitor's review of the event and event outcome, relationship of the event to the investigational product, and whether or not the research monitor concurs with the details of the study investigator's report.

Clinical Monitor: The designated clinical monitor for the trial is to:

1. Conduct initial, periodic, and termination clinical site visits;
2. Check that the clinical site is adhering to the protocol in its conduct of the study and to information presented in the informed consent documents, SOPs, and applicable regulations;
3. Oversee study file and regulatory documents, and cross check source documents and eCRFs; and
4. Observe study procedures.

Pharmacovigilance Physician:

The USAMMDA Safety PVG MD, as delegated by the sponsor, evaluates all safety cases and provides a final determination on relatedness to the product and whether expedited reporting is warranted per current FDA regulation and guidance. In coordination with USAMRMC USAMMDA ORA, each SAE report is reviewed for medical consistency, accuracy, and completeness and each event followed until it is satisfactorily resolved. In addition, the PVG MD will serve as an arbiter in cases where the PI and RM's review of these data results in discordant determinations.

The PVG MD is responsible for the review of SAE data and reports. In reviewing SAEs, the PVG MD will:

1. Review SAE reports to ensure the content is medically consistent, accurate, and complete;
2. Follow each SAE until it is satisfactorily resolved; and
3. Perform an assessment of the reporting status to the FDA/DSMB.

Data and Safety Monitoring Board: An independent DSMB will be convened to review clinical trial safety data and provide recommendations to the USAMMDA ORA PSSB. The PSSB will deliver the DSMB recommendations to the Sponsor's Representative for final decision. The USAMRMC USAMMDA ORA will communicate the final decision to the PI, who will notify the IRB. USAMRMC USAMMDA ORA will communicate the final decision to the FDA, as appropriate. A further description of the DSMB roles and responsibilities, functions, and reporting requirements is included in the DSMB charter.

10.1. Specification of Safety Endpoints

The investigator will review subjects' medical records and administer a focused review of systems and a physical examination to all subjects to determine the presence of symptoms or signs of coagulation abnormalities.

Primary safety endpoints will include those related to vital signs, clinical laboratory parameters (chemistry, hematology, urine analysis, and coagulation), and AEs.

10.1.1. Vital Signs

Vital signs to be measured include blood pressure, heart rate, respiration rate, and oral temperature. Vital sign measurements are collected at every on-site visit as part of the physical examination process. During and after the infusion process, vital sign measurements are used to observe for evidence of acute transfusion reactions (eg, bradycardia, tachycardia, cardiac dysrhythmia, hypertension, hypotension, fever, etc.) and are collected every 15 minutes (± 5 minutes) during the infusion, every 30 minutes (± 5 minutes) between 0 and 4 hours post-infusion, and then every 4 hours (± 40 minutes) until the subject is released from the clinic. Temperature will be standardly evaluated following HBC's SOP, Welch Allyn Spot Vital Sign Procedure (# WB-032-SOP).

10.1.2. Laboratory Assessments

Laboratory assessments should be performed whenever possible in a College of American Pathologists (CAP)/Clinical Laboratory Improvement Act certified environment or at least, following SOP-driven, QC-reviewed procedures.

The total amounts of blood drawn from a study subject who completes all study procedures are shown in Table 7 and Table 9.

10.1.2.1. Hematology and Clinical Chemistry

Table 11 summarizes the hematology and clinical chemistry markers that subjects will be tested for at the specified time points in the study.

Table 11: Hematology and Clinical Chemistry Tests

	Pre-Infusion			Post-Infusion					
HEMATOLOGY	**Screening**	**Collection Day**	**Infusion Day**	**0.5 Hours**	**4 Hours**	**24 Hours**	**7 Days**	**28 Days**	**Early Withdrawal**
CBC (Hematocrit, Hemoglobin, Platelet Count, RBC Count, WBC Count)	X		X	X	X	X	X	X	X
DAT (IgG and C3)	X		X			X		X	X
Hematocrit		X							
Cross-match RBC			X						
Reverse Type FDP/FFP			X						
Blood Type (ABO and Rh)	X		X						
Red-Cell Antibody Screen	X								
Syphilis Screen	X								
Screening Test for HTLV Antibody	X								
Nucleic Acid Tests for HIV-1/2, HBV, HCV, and West Nile Virus	X								
CLINICAL CHEMISTRY									
ALP	X		X	X	X	X	X		X
ALT	X		X	X	X	X	X		X
AST	X		X	X	X	X	X		X
Ionized Calcium; Total Magnesium			X	X					
Electrolytes (Calcium, Chloride, Potassium, Sodium, Lactate, Bicarbonate)	X		X	X	X	X	X		X
pH			X	X					
Glucose	X		X	X	X	X	X		X
Total Bilirubin	X		X	X	X	X	X		X
Total Protein	X		X	X	X	X	X		X
BUN	X		X	X	X	X	X		X
Creatinine	X		X	X	X	X	X		X
SPEP (All subjects undergoing plasmapheresis)		X							
Total Protein (All subjects undergoing multiple plasmapheresis sessions)		X							

10.1.2.2. Urinalysis

A clean-catch urine sample will be collected from all subjects at the screening visit to confirm study eligibility prior to enrollment. Additional urine samples will be collected from enrolled subjects on the day(s) they are infused and at the 24-hour post-infusion follow-up visit(s). The urinalysis will include:

- Visual exam – urine sample will be inspected for color and clarity; and
- Chemical exam – reagent test strips will be used to determine specific gravity, pH, as well as detect the presence of protein, glucose, ketones, blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen.

10.1.2.3. Coagulation Markers

Table 12 summarizes the coagulation markers subjects will be tested for at the specified time points in the study.

Table 12: Coagulation Tests

Coagulation Tests	Screening	Pre-Infusion	Post-Infusion				Early withdrawal
		Infusion Day	0.5 Hours	4 Hours	24 Hours	28 Days	
ALL SUBJECTS:							
PT/INR	X	X	X	X	X	X	X
aPTT	X	X	X	X	X	X	X
D-Dimer	X	X	X	X	X		X
COHORT 3 SUBJECTS ONLY:							
Factor I		X	X	X			X
Factor II		X	X	X			X
Factor V		X	X	X			X
Factor VII		X	X	X			X
Factor VIII		X	X	X			X
Factor IX		X	X	X			X
Factor X		X	X	X			X
Factor XI		X	X	X			X
von Willebrand Factor activity		X	X	X			X
Protein C activity		X	X	X			X
Protein S activity		X	X	X			X

10.1.2.4. Drug Screen

A urine drug screening will be performed for Cannabinoids, cocaine, amphetamines, opiates and PCP (NIDA-5) at the screening visit only. Potential subjects with a positive urine drug screen will be ineligible for enrollment.

10.1.2.5. Pregnancy Screen

An FDA-cleared qualitative urine pregnancy test that evaluates human beta-chorionic gonadotropin will be used to test all females (at screening, pre-infusion, and early withdrawal ONLY).

10.2. Investigational New Drug Safety Reporting

The following terms, as defined by 21 CFR 312.32, apply to this protocol.

10.2.1. Adverse Event or Suspected Adverse Reaction

An AE is defined as any untoward medical occurrence associated with the use of a drug/biologic in humans, whether or not it is considered to be related to the drug/biologic.

A suspected AR is any AE for which there is a reasonable possibility that the drug/biologic caused the AE. For the purposes of IND safety reporting, a "reasonable possibility" means there is evidence to suggest a causal relationship between the drug/biologic and the AE. Suspected AR implies a lesser degree of certainty about causality than AR, which means any AE caused by a drug/biologic.

An AE or suspected AR is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected AR that, had it occurred in a more severe form, might have caused death.

10.2.2. Serious Adverse Event or Serious Suspected Adverse Reaction

An AE is considered "serious" if, in the view of either the PI or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias

or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.2.3. Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An unexpected adverse event (UAE) or unexpected suspected AR is an AE that is not:

- Listed in the Investigator's Brochure (IB);
- Listed at the specificity or severity that has been observed; or
- Consistent with the risk information described elsewhere in the current application.

For example, if the IB referred only to elevated hepatic enzymes or hepatitis as expected AEs, under this definition, hepatic necrosis would be a UAE by virtue of the greater clinical severity. Similarly, if the IB only listed cerebral vascular accidents as an expected AE, the occurrence of cerebral thromboembolism and cerebral vasculitis would be a UAE by virtue of greater specificity. "Unexpected," as used in this definition, also refers to AEs or suspected ARs that are mentioned in the IB as occurring with a class of drugs/biologics or as anticipated from the pharmacological properties of the drug/biologic, but are not specifically mentioned as occurring with the particular drug/biologic under investigation.

10.2.4. Expected Adverse Events

An expected AE is a predetermined event, identified in the IB. The following expected AEs for this study include:

- Pain, bleeding, bruising, scarring, and local infection associated with fingerstick blood sampling procedures;
- Pain/soreness, bruising, discoloration, swelling, blood clot or bleeding, nerve damage, arterial puncture, local infection, dizziness, light-headedness, syncope, fatigue, iron deficiency with or without anemia associated with venipuncture;
- Blood loss from the inability to return RBCs during automated plasmapheresis procedures;
- Tingling of lips or fingers or muscle cramping, spasms, seizures, tetany, cardiac arrhythmia due to the citrate anticoagulant used in an automated plasmapheresis procedure;
- Allergic reactions such as flushing, itching, hives, abdominal cramps, difficulty breathing, chest pain, or bronchospasm, which may vary in severity from mild to life-threatening associated with both plasmapheresis donation and plasma infusion;
- Nausea, unpleasant taste, vomiting, light-headedness, fainting, malaise, or seizures associated with both plasmapheresis donation and plasma infusion;
- Non-immunologic complications such as the transmission of infectious agents, bacterial sepsis, transfusion-associated circulatory overload, hypothermia-cardiac arrhythmias;
- Metabolic complications such as citrate toxicity-hypocalcemia, acidosis, alkalosis, hyper-or-hypokalemia, and coagulopathies; and

- Transfusion reactions.

10.2.5. Unanticipated Problems Involving Risks to Subjects or Others

Federal regulations require that unanticipated problems involving risks to subjects or others be promptly reported to the IRB. These events encompass a broader category of events than SAEs, and may include issues such as problems with loss of control of subject data or the investigational product; adverse psychological reactions; or breach of confidentiality. Risks to others (eg, program personnel) must also be reported.

Unanticipated problems involving risks to subjects or others are any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the procedures that are described in the protocol, IB, or informed consent document; and (b) the characteristics of the subject population;
- Related or possibly related to a subject's participation in the study; and
- Suggests that the study places subjects or others at a greater risk of harm than was previously known or recognized.

The clinical site's IRB and the USAMRMC's HRPO will evaluate the PI's and RM's reports to determine whether or not a given incident, experience, or outcome constitutes an unanticipated problem involving risk to subjects or others, and will ensure reporting of the unanticipated problems involving risk to subjects or others to the appropriate regulatory offices, as applicable.

10.3. Relationship to Investigational Product

The site PI must assign a relationship of each AE to the receipt of the investigational product. The PI will use clinical judgment in conjunction with the assessment of a plausible biologic mechanism, a temporal relationship between the onset of the event in relation to receipt of the investigational product, and identification of possible alternate etiologies including underlying disease, concurrent illness, or concomitant medications. The following guidelines should be used to assess the relationship of an AE to study product administration and **ONLY A PHYSICIAN CAN MAKE THIS DETERMINATION:**

Not related: There is no reasonable causal relationship between the investigational product administered and the SAE. Applies to those events for which an alternate etiology exists.

Unlikely: Likely unrelated to the investigational product. Likely to be related to factors other than investigational product, but cannot be ruled out with certainty.

Possible: An association between the event and the administration of investigational product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology such as the subject's clinical status or underlying factors including other therapy.

Probable: There is a high degree of certainty that a relationship to the investigational product exists. There is a reasonable temporal association, and the event cannot be explained by known characteristics of the subject's clinical state or factors including other therapy.

Definite: An association exists between the receipt of an investigational product and the event. An association to other factors has been ruled out.

10.4. Severity Assessment

All AEs will be assessed for severity by the PI. Inherent in this assessment is the medical and clinical consideration of all information surrounding the event including any medical intervention required. The PI will use the CDC National Healthcare Safety Network Hemovigilance Module criteria (Appendix I) to define transfusion-related AEs.. The NCI Common Terminology Criteria for toxicity grade will be used to assign the severity for all AEs (transfusion and non-transfusion related) (HHS-2010). The criteria below may be used for any symptom not included in the grading scale. Any Grade 4 (life-threatening) or Grade 5 (fatal) AE must be reported as an SAE.

The eCRF for AEs will reflect only the highest severity for continuous days an event occurred.

Mild	Grade 1	Does not interfere with routine activities Minimal level of discomfort
Moderate	Grade 2	Interferes with routine activities Moderate level of discomfort
Severe	Grade 3	Unable to perform routine activities Significant level of discomfort
Life-threatening	Grade 4	Potentially life threatening or life-threatening and requires hospitalization, emergency room visit, or urgent intervention
Fatal	Grade 5	Death

The terms “serious” and “severe” are not synonymous. The term “severe” describes the intensity of a specific event (eg, mild, moderate, or severe headache), whereas the event itself may not meet the seriousness criteria.

If a subject is evaluated in an emergency room for non-life-threatening illness or symptoms (i.e., visits emergency department on weekend for mild problems because the physician’s office is closed), the information from that visit will be reviewed and severity of the AE will be assessed according to the subject’s clinical signs and symptoms.

As defined by the ICH guideline for GCP, the term “severe” is often used to describe intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself however, may be of relatively minor medical significance (such as severe headache). This is **not** the same as “serious,” which is based on subject/event **outcome** or **action** criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.5. Recording and Reporting Adverse Events

Section 6.6.3 presents procedures to request unblinding of a subject’s randomization code due to a medical emergency or serious medical condition.

10.5.1. Methods and Timing for Assessing, Recording, and Analyzing Adverse Events

All AEs will be assessed at all study visits, documented in the source records, and recorded on the eCRFs using accepted medical terms and/or the diagnoses that accurately characterize the event. When a diagnosis is known, the AE term recorded on the eCRF will be the diagnosis rather than a constellation of symptoms. The PI will assess and record for all AEs/SAEs: a description of the event (if the event consists of a cluster of signs and symptoms, a diagnosis should be recorded rather than each sign and symptom); onset date and time, and stop date and time; intensity (recorded as mild, moderate or severe); seriousness; causality (relationship to study drug); outcome (eg, resolved, resolved with sequelae, not resolved, fatal, or unknown if applicable); action taken with the study agent (eg, no action, study agent discontinued and other action taken).

When an event is not resolved by study closure, it will be documented on the AE eCRF as “"not recovered/not resolved".

AEs will be assessed using an open-ended question such as: “How have you been feeling since we last spoke?” If an AE that requires medical attention is reported to a nurse, it should be reported to a study physician immediately. The PI or study physician will assess subjects for any medical side effects, through a focused review of systems and physical exam. Specifically, they will be looking for evidence of coagulation disturbances. Subjects with suspected positive findings will be referred to their treating physicians for clinically indicated and appropriate evaluation and management. Acute plasma infusion reactions will also be specifically documented as follows:

- Fever (by oral or axillary temperature);
- Allergic reactions (i.e., skin rash; urticarial; pruritus; generalized flushing; localized angioedema; edema of the lips, tongue, or uvula; erythema of the periorbital area; conjunctival edema by physical exam);
- Bronchospasm (by symptoms);
- Chills (by subject report after specific query by clinical staff);
- Tachycardia, bradycardia, other dysrhythmias, dyspnea, hypertension, hypotension (by vital sign measurements – heart rate, blood pressure, and respiration rate);
- Hemolysis or acute hemolytic transfusion reactions resulting in circulatory/cardiovascular dysfunction (by clinical laboratory result); and
- Infection (by physical exam or clinical laboratory results).

The timeframe for the collection of AEs will begin at plasma collection and will continue through 7 days after the last required sample collection (Day 29). Any AE, regardless of its relationship to study product, will be recorded in the AE section of the eCRF. However, any AE that occurs after the informed consent is signed, but before the first infusion visit, will be recorded as medical history, unless it is related to a study procedure. AEs associated with a study procedure (eg, blood or plasma donation) will be recorded in the AE section of the eCRF.

10.5.2. Duration of Follow-Up of Subjects after an Adverse Event

PIs are required to follow SAEs to resolution, even if this extends beyond the prescribed reporting period or until study closure. Resolution is the return to baseline status or stabilization of the condition with the probability that it will become chronic. The SAE outcomes will be reported to the sponsor's Representative using the Serious Adverse Event Report Form (Appendix J).

Follow-up should be emailed to usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil or faxed using a new SAE Reporting Form. The follow-up form should state "this is a follow-up to the previously reported SAE" and provide the date of the original report. Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the participant continued or withdrew from study participation.

PIs are not obligated to actively seek SAEs in former subjects; however, if an SAE, considered to be related to the investigational product is brought to the attention of the PI *at any time* following completion of the study, the event will be reported to the sponsor's safety office as defined in section 10.6.1.

10.6. Reporting Adverse Events

The PI will report all AEs to the sponsor (USAMRMC ORA) and the local IRB in the appropriate safety, annual, and/or final reports. After appropriate data cleaning and query resolution between the clinical site, Clinical Monitor, and Clinical Data Manager, AEs marked as "serious" in the clinical database will be reconciled with the sponsor's SAE database. SAEs and AEs for inclusion in annual and final reports to the FDA will be provided from the clinical database by the Clinical Data Manager.

10.6.1. Reporting Serious Adverse Events

All SAEs must be reported promptly (within 24 hours of discovery of the event) to the sponsor's safety office as per 21 CFR 312.64 whether or not they are considered related to the study product. The completed SAE Reporting Form must be emailed to usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil or faxed within 24 hours of discovery of the event. Further, the investigator will comply with relevant study site SOPs on reporting SAEs to the IRB.

Contact information for reporting SAEs is provided in Table 13.

Table 13: Study Contacts for Reporting SAEs Involving Risk to Subjects or Others

Sponsor's Safety Office	USAMRMC ORA ATTN: MCMR-UMR 1430 Veterans Drive Fort Detrick, MD 21702-5009 Fax: 301-619-7790 Telephone: 301-619-1106 Email: usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil
IRB	University of Cincinnati University Hall, Suite 300 51 Goodman Drive PO Box 210567 Cincinnati, OH 45221-0567 Telephone: 513-558-5259 Email: irb@ucmail.uc.edu
USAMRMC Office of Research Protections	HRPO U.S. Army Medical Research and Materiel Command ATTN: MCMR-RPH 504 Scott Street Fort Detrick, MD 21702-5012 Fax: 301-619-7803 Telephone: 301-619-2165 Email: usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil
Research Monitor	Matthew Montgomery, MD Hoxworth Blood Center University of Cincinnati 3130 Highland Avenue, Cincinnati, OH 45267 Telephone: 513-558-1339 Fax: 513-558-1341 Email: montgmw@ucmail.uc.edu

Table 14: SAE Information to be Reported to the Sponsor's Safety Office

Notification Method	Information to be Provided
Email or Fax (within 72 hours)	Cover sheet or letter containing: IND number, sponsor study number, name of the investigational product, investigator name, and contact number
	Subject identification number
	Sponsor approved SAE Report Form documenting: SAE term and description, onset date, date(s) of investigational product administration, severity, relationship to study product, and subject's current status
	Concomitant medication CRF or a list of concomitant medications taken within 30 days of SAE onset
	Medical history Case Report Form
	Discharge summary and/or medical record progress notes, History and Physical, pertinent laboratory/diagnostic test results

NOTE: When submitting SAE reports via email, the subject line of each email notification will read as follows:

SAFETY REPORT – IND #____, Sponsor Study #____, Subject #____, Event term: ____

To comply with regulations mandating sponsor notification of specified SAEs to the FDA within 7 calendar days, the PI must submit additional information as soon as it is available. The sponsor or designee will report unexpected SAEs associated with the use of the study product to the FDA as specified at 21 CFR 312.32 (c).

The PI must follow all relevant regulatory requirements as well as specific policy regarding the timely reporting of SAEs to the RM, the local IRB, and the USAMRMC ORP.

Reporting to the sponsor's safety office does not fulfill the PI's duty to report all unanticipated problems involving risk to human subjects or others to the IRB. The PI will notify the local IRB, the USAMRMC ORP, and the RM.

10.6.2. Reporting to the IRB

Unanticipated problems involving risk to subjects or others, SAEs related to participation in the study, and all subject deaths related to participation in the study should be promptly reported by the PI via telephone, email, or fax to the local IRB and/or USAMRMC HRPO. A complete written report should follow the initial notification.

The PI is required to forward safety information provided by the sponsor or designee to the IRB, following the institutional policies.

10.6.3. Reporting Additional Immediately Reportable Events to the Sponsor's Safety Office

10.6.3.1. Pregnancy

Each pregnancy (for subjects and for female partners of participating male subjects) must be reported by the PI **within 72 hours of identification** by emailing the Pregnancy Report Form

(FORM.5.2.4) (Appendix K) to the sponsor's safety office (ORA). The incident must also be reported to the local IRB and/or the USAMRMC ORP in accordance with the IRB policy.

Subjects who become pregnant after receipt of investigational product will be withdrawn from the study and followed to term. The following information will be gathered, documented, and reported on the follow-up Pregnancy Report Form: outcome; date and type of delivery; APGAR scores; and health status of mother and child, including the child's gender, height, and weight. Complications and/or abnormal outcomes should be reported including any premature terminations, and are to be followed as above under the AE section. A pregnancy is reported as an AE or SAE only when there is suspicion that the investigational product may have interfered with the effectiveness of contraception or there was a serious complication in the pregnancy, including a spontaneous abortion, an elective termination for medical rationale, or the infant has a congenital anomaly/birth defect.

10.6.3.2. AE-Related Withdrawal of Consent

Any AE-related withdrawal of consent during the study must be reported by the PI immediately **(within 72 hours of identification)** by email or fax to the sponsor's representative, CRO's PI. The incident must also be reported to the local IRB and/or the USAMRMC ORP in accordance with the IRB policy.

10.6.4. Pending Inspections/Issuance of Reports

The knowledge of any pending compliance inspection/visit by the FDA, Office for Human Research Protections, HHS, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any regulatory agency including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to the local IRB and/or the USAMRMC ORP.

10.6.5. IND Annual Report to the FDA

The sponsor or designee will be responsible for the preparation of a detailed annual synopsis of clinical activity, including AEs. The sponsor or designee will deliver the annual report to the FDA. Each annual report will summarize IND activity for 1 year beginning approximately 3 months before the IND FDA anniversary date. The report will include, but is not limited to, summaries of all reported SAEs, submitted IND safety reports, number of subject withdrawals with reasons, updates to the general investigation plan, updates to the IB, and any protocol updates. The sponsor's representative or designee will notify the PI of the due date allowing sufficient time to assemble the required information.

10.6.6. Final Report

A final study report will be prepared by the sponsor's representative or designee in accordance with "Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications" and ICH E3 Guideline "Structure and Content of Clinical Study Reports."

The report will provide a description of the conduct of the study and will be accompanied by tables, listings, and figures (displaying all study data and results).

This final report will be submitted to the FDA.

The clinical site's local IRB may request a summary of study activities on a regular basis. The sites should comply with their local IRB requirements for the submission of safety, annual, and/or final reports.

11. STATISTICS

Detailed statistical procedures, listings, table shells, and figures will be provided in a separate statistical analysis plan (SAP). The SAP will be finalized before study close-out and database lock. The following key statistical components will be considered and a detailed description will be documented in the SAP:

- Primary and secondary endpoints and how they will be measured;
- Statistical methods and tests that will be used to analyze the endpoints; and
- Planned exploratory analyses and justification of their importance.

11.1. Description of Statistical Methods and Analysis

The primary objective of this study is to assess the safety of single infusions with RePlas™ FDP product at increasing fixed doses of either 1 unit (approximately 270 mL), 2 units (approximately 540 mL), or 3 units (approximately 810 mL) in normal healthy subjects. Safety will be assessed by evaluating vital signs, laboratory tests during and after infusion, FDP-related AEs. No formal statistical hypotheses will be tested. Demographics, medical history, and safety data will be summarized for each cohort using standard descriptive statistics. For quantitative variables, summaries will include the sample size, mean, median, standard deviation, minimum, maximum and 25th and 75th percentile. For categorical variables, summaries will include the frequency (eg, number and percent) of subjects for each outcome. Additional analytic data will be prepared and summarized using only Cohort 3 data to address the study's secondary objectives.

The demographic and subject disposition tables will include all 5 populations per Section 11.7. If it is shown that both full populations include the same subjects, only one table will be produced with the title indicating that it represents both full populations. AE tables that display overall AE incidence will include all 5 populations. Tables that are restricted to TEAEs will include the safety populations only. Study drug exposure will be presented in the first safety population. All other analyses will be performed in the third safety population only.

After the completion of each cohort and at the conclusion of the study, the DSMB will review all subjects' cumulative safety data and make a recommendation to the sponsor on whether or not to proceed to the next cohort and for cohort 3 to proceed with conducting the next planned FDP trial protocol.

11.1.1. Endpoints for Primary Study Objective Analyses

The primary endpoints for the study to be assessed are specifically:

- TEAEs;
- SAEs;

- Suspected, unexpected, serious adverse reactions (SUSARs); and
- Deaths.

Safety endpoints for subjects' that will be assessed just prior to infusion and again after infusion include evaluations presented in sections 8.2 and 8.3.

Descriptive statistics will be used to analyze the primary safety endpoints. Tables produced to exhibit the primary safety endpoint data will be presented by the specific type of plasma product infused. In Cohorts 1 and 2, this data will be presented by FDP product type, FDP-ACD and FDP-CPD; in Cohort 3 by experimental product and control product, FDP-ACD and FFP. The primary safety data reported to the DSMB for Cohort 3 will be masked. Unblinding during the study will only occur in accordance with section 6.6.3.

In general, AEs that occur in Cohort 3 subjects within 14 days after infusion will be attributed to the most recently infused product. However, there may be exceptions to use of this temporal attribution rule to all transfusion-related AEs given the possibility that those AEs that occur after infusion with the second product may potentially be related to infusion with the first infusion product (e.g., an immunogenic response).

The safety endpoints measured prior to the infusion will serve as the "baseline" to which all subsequent measurements will be compared.

11.1.2. Endpoints for Secondary Study Objectives Analyses

11.1.2.1. Safety Analyses Comparing FDP to FFP (Secondary Objective #1):

Using Cohort 3 data, descriptive statistics similar to those described in section 11.1.1 will be presented for the change between baseline and each time point, where appropriate, of the safety endpoint measures shown in Table 15. Descriptive statistics will be provided for each type of plasma product treatment, treatment period, and treatment sequence arm (FDP-ACD then FFP [Sequence 1] or FFP then FDP-ACD [Sequence 2]). The mean and standard deviation at each time point for each treatment group, based on the original values, will be exhibited in figures. Color-coded spaghetti plots will display by treatment group individual data for each subject over time.

Definitions for Secondary Objectives:

- Change from baseline: (Post-baseline value – baseline value);
- Body mass index (kg/m2): (weight (kg)/(height (cm) *100)2; and
- Total amount administered per kg of weight (ml/kg): total amount administered (ml)/weight (kg).

The secondary endpoints for this study and associated time points for analysis are listed in Table 15.

Table 15: Secondary Safety Endpoints and Scheduled Measurements

Safety Endpoints	Pre-Infusion	Post-Infusion			
		0.5 Hours	4 Hours	24 Hours	28-Day
Vital Signs					
Blood Pressure	X	X	X		
Heart Rate	X	X	X		
Respiration Rate	X	X	X		
Temperature	X	X	X		
Urinalysis:					
Specific gravity	X	X	X		
pH	X	X	X		
Glucose	X	X	X		
Ketones	X	X	X		
Protein	X	X	X		
Blood	X	X	X		
Leukocyte esterase	X	X	X		
Nitrite	X	X	X		
Bilirubin	X	X	X		
Urobilinogen	X	X	X		
CBC					
Hematocrit	X	X	X	X	
Hemoglobin	X	X	X	X	
Platelet Count	X	X	X	X	
RBC Count	X	X	X	X	
WBC Count	X	X	X	X	
DAT (IgG and C3)	X			X	
Clinical Chemistry					
ALP	X	X	X		
ALT	X	X	X		
AST	X	X	X		
Ionized Calcium	X	X			
Total Magnesium	X	X			
pH	X	X			

Safety Endpoints	Pre-Infusion	Post-Infusion			
		0.5 Hours	4 Hours	24 Hours	28-Day
Electrolytes (Calcium, Chloride, Potassium, Sodium, Lactate, and Bicarbonate)	X	X	X		
Glucose	X	X	X		
Total Bilirubin	X	X	X		
Total Protein	X	X	X		
BUN	X	X	X		
Creatinine	X	X	X		
Coagulation Tests					
PT	X	X	X	X	X
INR	X	X	X	X	X
aPTT	X	X	X	X	X
D-dimer	X	X	X	X	
Cohort 3 safety analyses will also include measurements taken at each Infusion Visit at the following post-infusion time points.					
Factor I	X	X	X		
Factor II	X	X	X		
Factor V	X	X	X		
Factor VII	X	X	X		
Factor VIII	X	X	X		
Factor IX	X	X	X		
Factor X	X	X	X		
Factor XI	X	X	X		
von Willebrand Factor activity	X	X	X		
Protein C activity	X	X	X		
Protein S activity	X	X	X		
PF 1+2	X	X			
TAT	X	X			
Antithrombin III	X	X			
Alpha-2 Antiplasmin	X	X			
C3a des Arg	X	X			

11.1.2.2. Exploratory Analyses Comparing FDP to FFP (Secondary Objective 2)

The analyses conducted for secondary objective 1 will be used to meet secondary objective 2. In addition, descriptive statistics on a post-infusion, abnormal coagulation function assay that is greater than a 20% change in either direction from baseline for PT/INR and/or aPTT values will be presented using separate shift tables. Shift tables based on the upper limit of normal (ULN) will also be provided for D-dimer, PF 1+2, TAT, and C3a des Arg.

11.1.3. Safety Analyses

AEs will be coded using the most recent version of the Medical Dictionary of Regulatory Activities preferred terms and will be grouped by system, organ, class designation (SOC).

AEs will be summarized using standard FDA-recommended templates distinguishing those defined as TEAEs. A TEAE will be defined as an AE that emerges during or following treatment (infusion), having been absent pretreatment. For all TEAEs, relatedness to infused product will be presented. TEAEs related to study treatment will be defined as definitely or probably related to study treatment.

Use of the Centers for Disease Control National Healthcare Safety Network Hemovigilance Module criteria will ensure consistent definitions are applied when using transfusion-related event terms, such as transfusion related acute lung injury or transfusion associated circulatory overload. The National Cancer Institute Common Terminology Criteria will be used to assess all AEs for toxicity grade, or severity, regardless of whether the event is transfusion-related (HHS-2010). AEs will also be presented by maximum severity or maximum common terminology criteria for AE (CTCAE) grade (depending on collection). A summary of SAEs and a summary of AEs leading to treatment discontinuation will be presented.

11.2. Planned Enrollment and Reason for Sample Size

The sample size for this single-site study is set to 24. The primary objective of this study is to assess the safety of single infusions with the RePlas FDP product at increasing fixed doses of either 1 unit (approximately 270 mL), 2 units (approximately 540 mL), or 3 units (approximately 810 mL) in normal healthy subjects. Safety will be measured using the following primary safety endpoints: AEs, TEAEs, SAEs, SUSARs, and deaths. The sample size was selected to reasonably balance the ability to address the study's primary objective while minimizing the number of subjects potentially at risk. Precision estimates were calculated using different safety outcome incidence rates and different sample sizes as exhibited in Table 16. For example, in 24 subjects, a safety outcome with an incidence rate of 10% would have a 95% confidence interval of 1.6-29.2% and a corresponding width=27.6 at a 2-sided alpha of 0.05. To account for subject attrition and for comparison purposes, a sample size of 20 and 28, are, respectively, included in Table 16.

Concurrent infusions will not take place across cohorts ensuring infusions at the next higher dose do not begin until all subject infusions at the previous dose have been completed. The duration for which each cohort will remain active has been estimated based on the study schedule such that Cohorts 1 and 2 are expected to each be active for approximately 6 months and Cohort 3 will be active for approximately 7 months.

Sections 5.10 and 7.1 contain information on the capabilities of HBC to recruit the required number of subjects for this study.

Table 16: Precision Estimates Based on Safety Outcome Incidence Rates and Sample Size

Sample Size	Incidence		
	10%	**25%**	**50%**
20	(1.2-31.7) δ=30.5	(8.7-49.1) δ=40.4	(27.2-72.8) δ=45.6
24	(1.6-29.2) δ=27.6	(9.8-46.7) δ=36.9	(29.1-70.9) δ=41.8
28	(2.0-27.3) δ=25.4	(10.7-44.9) δ=34.2	(30.6-69.4) δ=38.7

11.3. Level of Significance

The level of significance does not apply since no statistical testing will be done in this study.

11.4. Interim Analysis and Stopping Rules

The SRs for the study are presented in section 6.5. No interim analysis is planned for this study.

At the conclusion of each cohort and after Cohort 3 study activities, the DSMB will review all patient safety data and make a recommendation to the sponsor on whether to proceed with dose escalation in the subsequent cohort and after cohort 3 with the next planned FDP trial protocol as mentioned in section 11.1. No adjustment for multiple testing is necessary since no statistical hypotheses are being tested. (The planned descriptive analyses are described in section 11.1.)

11.5. Accounting for Missing, Unused, and Spurious Data

Non-analyzable data will be documented in the deviations and reported in the final clinical study report.

For summary descriptive statistics, missing data will be represented by counts.

11.6. Procedures for Reporting Deviations from the Original Statistical Plan

Any deviation(s) from the original statistical plan as indicated in the protocol will be described in an amendment to the protocol and the SAP. Deviations from the SAP will be documented in accordance with the data management center's SOPs.

11.7. Selection of Subjects to be Included in Analyses

Healthy male and female volunteers determined to be acceptable WB or plasmapheresis donors based on FDA regulations and responses to the AABB donor history questionnaire (Appendix B) of the protocol) are eligible to provide study consent. In addition, the study considers those deferred from donating due only to travel, as outlined by the AABB donor history questionnaire,

as eligible to consent for potential study enrollment. All subjects subsequently enrolled must meet the study inclusion and exclusion criteria, detailed in sections 7.4 and 7.5 of the protocol.

There will be 5 analysis populations for this study, 2 full analysis populations, and 3 safety populations.

The full analysis population encompasses all enrolled subjects, including those who were:

- Enrolled but withdrawn from the study prior to the Infusion Visit and were never infused; and
- Enrolled and presented for treatment at the Infusion Visit (includes infused and not infused).

The 3 subject populations for assessing safety are those who:

- Received any volume of infused product (ie, In Cohort 3 subjects this includes those who received a partial dose at either Infusion Visit);
- Received the full infusion dose and had at least one outcome measure; and
- Received the full infusion dose and can be fully evaluated because:
  - Cohort 1 and 2: the subjects completed, at a minimum, the 7-Day Follow-Up Visit; and
  - Cohort 3: the subjects had both complete infusion doses and completed, at a minimum, the 7-Day Follow-Up Visit after the second infusion.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject. Representatives of USAMRMC, the sponsor's representative, the local IRB, the USAMRMC ORP, and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research. Personal identifiers will be removed from photocopied medical and research records. Study results will not be given to individual subjects, but will be published in the open literature and made available as a matter of public record.

12.1. Study Monitoring

Study monitoring will be the responsibility of the USAMRMC USAMMDA ORA designee, an independent contract research organization. Upon successful approval of the protocol and establishment of the regulatory file, the clinical monitor will establish a clinical monitoring plan. To ensure that the PI and the study staff understand and accept their defined responsibilities, the clinical monitor will maintain regular correspondence with the clinical site and may be present during the course of the study to verify the acceptability of the facilities, compliance with the investigational plan and relevant regulations, and the maintenance of complete records.

Monitoring visits by a sponsor's representative-designated clinical monitor will be scheduled to take place at the initiation of the study, during the study at appropriate intervals, and after the last subject has completed the study. A report of monitoring observations will be provided to the PI (for corrective actions), USAMRMC USAMMDA ORA, USAMMDA Office of Quality Management, and the Product Manager.

12.2. Audits and Inspections

Authorized representatives of the sponsor, the FDA, and the IRB may visit the clinical site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether or not these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guideline of the ICH, and any applicable regulatory requirements.

The PI should contact the sponsor's representative and ORP HRPO immediately if contacted by a regulatory agency about an inspection.

12.3. Institutional Review Board

The HBC IRB will serve as the responsible IRB and will review the protocol, informed consent, and progress reports on a continuing basis in accordance with all applicable regulations, including Title 21 CFR 50 and 56.

The PI must obtain IRB approval for the study. Initial IRB approval, and all materials approved by the IRB for this study, including the subject consent form and recruitment materials, must be maintained by the PI and made available for inspection.

The PI will be responsible for preparing and submitting continuing review reports per institution and IRB requirements. The PI or a designee will transmit the approved final study report to the IRB as soon as the documents are available.

13. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor's Representative may conduct quality assurance audits. Refer section 12.2 for more details regarding the audit process.

Auditing of the clinical trial may be conducted at any time during the study to ensure continued compliance with regulations, policies, and procedures. Auditing will be undertaken, as needed, by independent personnel designated by the Office of Quality Management, USAMMDA. Audit findings will be documented in a formal audit report that will detail the conduct of the audit and summarize the observations noted.

14. ETHICS

14.1. Ethics Review

The study is based on adequately performed laboratory and animal experimentation and will be conducted under a protocol reviewed by the local IRB and ORP. The study is to be conducted by scientifically and medically qualified persons. The IRB will determine whether or not the benefits of the study are in proportion to the risks. The rights and welfare of the subjects will be respected; the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits; the results to be reported will be accurate; subjects will give their informed consent and will be competent to do so and not under duress; and all study staff will comply with the ethical principles in 21 CFR Part 50 and the Belmont Principles.

14.1.1. Review/Approval of Study Protocol

Before a clinical study can be initiated, the study protocol and other required documents will be submitted to the following departments in the order listed for review and/or approval, with the final review by the FDA:

- Integrated Product Team;
- Sponsor's Representative Team (USAMRMC USAMMDA ORA);
- Local IRB and the ORP;
- Sponsor's Representative (acting for The Surgeon General [TSG] of the Army); and
- USAMRMC Commanding General, if applicable.

Enrollment in this protocol may not begin until all approvals have been obtained and the formal authorization letter is received by the PI from the sponsor's representative.

14.1.2. Protocol Modifications

All modifications to the protocol and supporting documents (informed consent, study-specific procedures, SOPs, recruitment materials, etc.) must be reviewed and approved prior to implementation. Any protocol amendment will be agreed upon and approved by the sponsor's representative prior to submission to the local IRB and prior to implementation of said change or modification. Any modification that could potentially increase risk to subjects must be submitted to USAMRMC ORP and the FDA prior to implementation. The ICF must be revised to concur with any amendment as appropriate and must be reviewed and approved with the amendment. Any subject already enrolled in the program will be informed about the revision and asked to sign the revised informed consent document if the modification directly affects the individual's participation in the program. A copy of the revised, signed, and dated informed consent document will be given to the subject. All original versions of the informed consent document will be retained in the protocol regulatory file, and a copy will be retained in the protocol regulatory file.

14.1.3. Protocol Deviation Procedures

All deviations from the protocol (eg, failure to return for follow-up visits or blood collection within the time indicated in the protocol) are to be documented. The PI or designee will be

responsible for identifying and reporting all deviations, which are defined as isolated occurrences involving a procedure that did not follow the study protocol. Deviations will be reported annually in the continuing review report to the local IRB and the ORP and, if appropriate, in the final study report. Action taken in response to the deviation, and the impact of the deviation will be assessed by the PI and recorded as significant or nonsignificant.

Any protocol deviation that adversely affects the safety or rights of a subject or scientific integrity of the study will be reported immediately to the sponsor's representative, local IRB, and the ORP.

14.2. Ethical Conduct of the Study

This study will be conducted in accordance with all applicable Federal and DoD human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice.

The procedures set out in this study are designed to ensure that the sponsor's representative and all study personnel abide by the principles of the ICH GCP guideline and the CFR. The PI confirms this by signing this study protocol and the Form FDA 1572.

14.2.1. Confidentiality

The Health Insurance Portability and Accountability Act (HIPAA) requires that researchers obtain the subject's permission (HIPAA Authorization) to use and disclose health information about the subject that is either created by or used in connection with this research. The information includes the entire research record and supporting information from the subject's medical records, results of laboratory tests, and both clinical and research observations made during the individual's participation in the research.

In this research, the subject's health information will be collected and used to conduct the study; to monitor the subject's health status; to measure effects of the investigational product; to determine research results; and possibly to develop new tests, procedures, and commercial products. Health information is used to report results of research to the sponsor's representative and Federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. After the study ends, each subject has the right to see and receive a copy of his or her information.

Representatives of the TSG as the IND sponsor, the sponsor's representative, the local IRB, the ORP, the DoD, and the FDA are eligible to photocopy and review records related to this protocol as a part of their responsibility to protect the subjects of this protocol. In addition, these representatives are eligible to witness the applicable study procedures to ensure the safety of subjects.

No personal identifier will be used in any publication or communication used to support this research study. The subject's identification number will be used in the event it becomes necessary to identify data specific to a single subject.

14.2.2. Compensation for Participation

Subjects will be compensated for time and travel expenses for participating in this study in accordance with local IRB policies and as described in the ICF.

14.2.3. Medical Care for Research-Related Injury

All non-exempt research involving human subjects shall, at a minimum, meet the requirement of 32 CFR 219.116(a)(6).

If a subject is injured because of participation in this research, emergency medical care will be provided. However, since there is no reimbursement available by the Department of Defense (DoD) or the non-DoD clinical site for medical expenses incurred to treat research-related injuries, subjects or their individual insurance companies may be responsible for these medical expenses. Subjects are waiving no legal rights by participation in the study and will only be treated for injuries directly caused by the research study.

14.3. Written Informed Consent

The informed consent process and document will be reviewed and approved by the local IRB and/or the ORP and sponsor's representative prior to initiation of the study. The consent document contains a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with 21 CFR 50. The consent document indicates that by signature, the subject, or where appropriate, legal guardian, permits witnessing of applicable study procedures by the sponsor's representative, as well as access to relevant medical records by the sponsor's representative and by representatives of the FDA. The sponsor's representative will submit a copy of the initial IRB- and sponsor's representative-approved consent form to the FDA and will maintain copies of revised consent documents that have been reviewed and approved by the local IRB and/or the ORP.

A written informed consent document, in compliance with 21 CFR Part 50, 32 CFR Part 219, and the Belmont Principles and HIPAA Authorization will be signed by the subject before any study-related procedures are initiated for that subject. This consent document must be retained by the PI as part of the study records. Each subject will receive a copy of the signed informed consent document. The PIs or their designees will present the protocol in lay terms to individual subjects. Questions on the purpose of the protocol, protocol procedures, and risks to the subjects will then be solicited. Any question that cannot be answered will be referred to the PI. No subject should grant consent until questions have been answered to his or her satisfaction. The subject should understand that the study product is an investigational drug and is not licensed by the FDA for commercial use, but is permitted to be used in this clinical research. Informed consent includes the principle that it is critical the subject be informed about the principal potential risks and benefits. This information will allow the subject to make a personal risk versus benefit decision and understand the following:

- Participation is entirely voluntary;
- Subjects may withdraw from participation at any time;
- Refusal to participate involves no penalty; and
- The individual is free to ask any questions that will allow him or her to understand the nature of the protocol.

Should the protocol be modified, the subject consent document must be revised to reflect the changes to the protocol. If a previously enrolled subject is directly affected by the change, the

subject will receive a copy of the revised informed consent document. The approved revision will be read, signed, and dated by the subject.

The subject will be informed that a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US law.

15. DATA HANDLING AND RECORDKEEPING

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the PI(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study. The source documents will be retained at the clinical site. Any paper records will be stored in a locked file cabinet with access limited to the PI. A subject identification list will be maintained in a separate, secure file.

For this study, an Electronic Data Capture (EDC) database system will be used for the collection of the study data in an electronic format. The EDC database system will be designed based on the protocol requirements, the approved eCRF layouts and specifications, and in accordance with 21 CFR Part 11. The eCRF layouts and specifications define and identify the applicable source data that will be collected and captured into the EDC database system. The applicable source data will be electronically transcribed by the clinical site designee onto the eCRF (data entry screens) in the EDC database system. The PI is ultimately responsible for the accuracy of the data transcribed on the eCRF. Data monitoring and management will be performed in the EDC database system by the study clinical monitor and the designated data management group.

A detailed data management plan will be written and approved by the study team and the PI prior to study start, with approval by the sponsor's data manager in the USAMRMC USAMMDA ORA. All updates to the data management plan must be approved before study close-out and database lock.

15.1. Inspection of Records

The sponsor's representative or designee will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The PI agrees to allow the clinical monitor to inspect the drug storage area, investigational product stocks, drug accountability records, subject charts, study source documents, and other records relative to study conduct.

Subjects' health information is used to report results of research to the sponsor's representative and Federal regulators, and may be reviewed during study audits for compliance with study plans, regulations, and research policies. The consent document indicates that by signature, the subject permits access to relevant medical records by the sponsor's representative and by representatives of the FDA.

Upon a subject's termination from the trial, completed eCRFs will be ready and available for on-site review by the sponsor's representative or the designated representative within 14 days after receipt of the subject's data.

15.2. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, for 2 years following the discontinuance of the investigational product for investigation. If it becomes necessary for the sponsor's representative or designee or the FDA to review any documentation relating to the study, the PI must permit access to such records.

Completed, monitored eCRFs will be stored in a secure location by the sponsor's representative or designee. A copy of each completed eCRF will be retained by the PI.

The PI will be responsible for retaining sufficient information about each subject, including the name, address, telephone number, Social Security Number, and subject identifier in the study, so that the sponsor's representative, the local IRB, the FDA, employees of USAMRMC, or other regulatory authorities may have access to this information, should the need arise.

It is the policy of USAMRMC that data sheets are to be completed for all subjects participating in research (Form 60-R, Volunteer Registry Data Sheet). The data sheets will be entered into this Command's Volunteer Registry Database. The information to be entered into this confidential database includes the subject's name, address, and Social Security Number; study title; and dates of participation. The intent of this database is twofold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that USAMRMC can exercise its obligation to ensure research subjects are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years. The Volunteer Registry Database is a separate entity and is not linked to the study database.

16. PUBLICATION POLICY

All data collected during this study will be used to support this IND. All data may be published in the open medical or military literature with the identity of the subjects protected. Anyone desiring to publish or present data obtained during the conduct of the study will conform to the author's local publication review authority's policies and then forward the publication for review to the Commander, USAMMDA or designee and usarmy.detrick.medcom-usamrmc.list.clearances@mail.mil prior to submission.

17. LIST OF REFERENCES

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18. APPENDICES

APPENDIX A. STUDY PERSONNEL ROLES AND RESPONSIBILITIES

Principal Investigator: The PI will have overall responsibility for the study and for compliance with the GCP guideline. The PI will conduct the study according to the investigational plan, institutional policies, and all applicable regulations. The PI will comply with the PI's agreement (Form FDA 1572), supervise the use of the test articles, and maintain accurate study records. The PI will permit and comply with audits and monitoring requirements. The PI will report all SAEs to appropriate regulatory bodies, including the local IRB, as required; the sponsor's representative through the USAMRMC USAMMDA ORA; the RM, and the USAMRMC ORP.

Clinical Research Coordinator: The clinical site clinical research coordinator will be responsible for quality control on all aspects of the study, to include sample collection, volunteer records, source documents and eCRFs, regulatory binders, and data sheets. The clinical research coordinator will maintain regulatory files, host visits of auditors, monitor all inspections, coordinate routing of all protocol activity, and maintain and update files of study staff curriculum vitae and GCP training certificates.

Research Staff: The research staff will assist in the preparation of the protocol, eCRFs, and other associated documents as needed, monitor various aspects of the study, review information on eCRFs to ensure data are complete and correct, and assist in rectifying discrepancies on eCRFs; maintain study records and logs; assist in evaluating study results and preparing reports; ensure that volunteers have read and understand the informed consent document and have had all questions appropriately answered; ensure that informed consent documents are properly signed and dated; collect pre-and post-infusion vital signs, conduct blood draws, and collect and ensure the integrity of blood samples; collect and record AEs and follow up and consult with PIs on all moderate and severe AEs; and assist the Protocol Administrator with maintenance of regulatory files and update all study staff curriculum vitae and GCP training certificates.

Clinical Monitor: Study clinical monitoring will be the responsibility of the USAMRMC USAMMDA ORA designated clinical monitor. The clinical monitor will conduct initial, periodic, and termination study site visits; check protocol adherence including adherence with information presented in the informed consent documents, SOPs, and applicable regulations; oversee study file and regulatory documents, cross check source documents and eCRFs; confirm procedures for the storage, dispensation, and destruction of investigational product are in compliance with the study protocol; and observe study procedures.

Research Monitor: The RM is affiliated with the clinical site where the trial is taking place but is not otherwise involved with this protocol. The RM is a safety advocate for study subjects and as such, will review all AEs, SAEs, treatment emergent adverse events (TEAEs), protocol violations, and annual reports. For the first 5 subjects in each cohort, the RM will individually review each subject's data through the 24-hour post-infusion follow-up visit prior to the infusion of the subsequent subject. The RM will look for any signs of SAEs or AEs that meet SR criteria. The RM is required to review all unanticipated problems involving risk to study volunteers, other SAEs, and any volunteer deaths associated with the protocol and to provide an unbiased written report of the event. The RM may discuss the protocol with study investigators, interview subjects, and consult with others outside the study about the research and is authorized to stop the protocol, remove subjects from the protocol, and take any necessary steps to protect the safety and well-being of subjects until the IRB can assess the RM's report.

The RM's report, at a minimum, is to provide comment on the outcomes of the event or problem and, in the case of an SAE or death, comment on the event's relatedness to study participation. The RM should also indicate whether or not he or she concurs with the details of the report provided by the study PI. Reports of events determined by either the PI or the RM to be possibly or definitely related to participation, and reports of events resulting in death should be promptly forwarded to appropriate regulatory bodies, including the sponsor's representative through USAMRMC USAMMDA ORA; Westat's PI; and USAMRMC ORP.

Clinical Data Manager: The data management center will be responsible for the oversight of the development of the study eCRFs, database design and validation, data management plan, and for performing data quality/data cleaning activities.

Biostatistician: Biostatisticians, employed by the data management center, will assist in the design and development of the protocol and the study database. The biostatisticians will prepare the study SAP, perform statistical analyses, and review the study final report.

Product Manager: The product manager will be responsible for the overall management of the product development effort.

Regulatory Affairs Scientist: The regulatory affairs scientist conducts all regulatory reviews and obtains the IND sponsor representative's approval and is responsible for all submissions to and all communications with the US FDA.

Pharmacovigilance Physician: The USAMMDA PVG MD, part of the USAMRMC USAMMDA ORA staff, will serve as an arbiter in cases where the PI and RM's review of these data results in discordant determinations. In addition, the PVG MD evaluates all SAEs and provides the final determination on relatedness to the product, and whether expedited reporting is warranted, per current FDA regulation and guidance.

The PVG MD is responsible for integrating the review of safety data regarding SAEs and reviewing each SAE report. In reviewing SAEs, the PVG MD will:

1. Review submitted SAE safety reports to ensure the content is medically consistent, accurate, and complete;
2. Follow each event until it is satisfactorily resolved; and
3. Perform an assessment of the reporting status to the FDA/DSMB.

Quality Assurance Support: Quality Assurance support may be asked to perform audits to verify compliance to the protocol and other requirements of this study.

Clinical Trial Manager: The clinical trial manager coordinates development of the protocol and protocol amendments, coordinates review of the protocol and all protocol-related documents; and coordinates completion of the study start and study close out checklists.

APPENDIX B. AABB FULL-LENGTH DONOR HISTORY QUESTIONNAIRE

The questionnaire provided here is a sample and may have undergone revisions since the protocol was drafted. Only the most recent version in use at the clinical site will be administered to study subjects.

	Yes	No	
Are you			
1. Feeling healthy and well today?	☐	☐	
2. Currently taking an antibiotic?	☐	☐	
3. Currently taking any other medication for an infection?	☐	☐	
Please read the Medication Deferral List.			
4. Are you now taking or have you ever taken any medications on the Medication Deferral List?	☐	☐	
5. Have you read the educational materials?	☐	☐	
In the past **48 hours**			
6. Have you taken aspirin or anything that has aspirin in it?	☐	☐	
In the past **6 weeks**			
7. Female donors: Have you been pregnant or are you pregnant now? (Males: check "I am male.")	☐	☐	☐ I am male
In the past **8 weeks have you**			
8. Donated blood, platelets, or plasma?	☐	☐	
9. Had any vaccinations or other shots?	☐	☐	
10. Had contact with someone who had a smallpox vaccination?	☐	☐	
In the past **16 weeks**			
11. Have you donated a double unit of red cells using an apheresis machine?	☐	☐	
In the past **12 months have you**			
12. Had a blood transfusion?	☐	☐	
13. Had a transplant such as organ, tissue, or bone marrow?	☐	☐	
14. Had a graft such as bone or skin?	☐	☐	
15. Come into contact with someone else's blood?	☐	☐	
16. Had an accidental needlestick?	☐	☐	
17. Had sexual contact with anyone who has HIV/AE or has had a positive test for the HIV/AE virus?	☐	☐	
18. Had sexual contact with a prostitute or anyone else who takes money or drugs or other payment for sex?	☐	☐	

19. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything not prescribed by their doctor?	☐	☐	
20. Had sexual contact with anyone who has hemophilia or has used clotting factor concentrates?	☐	☐	

In the past **12 months have you** (continued)	Yes	No	
21. Female donors: Had sexual contact with a male who has ever had sexual contact with another male? (Males: check "I am male.")	☐	☐	☐ I am male
22. Had sexual contact with a person who has hepatitis?	☐	☐	
23. Lived with a person who has hepatitis?	☐	☐	
24. Had a tattoo?	☐	☐	
25. Had ear or body piercing?	☐	☐	
26. Had or been treated for syphilis or gonorrhea?	☐	☐	
27. Been in juvenile detention, lockup, jail, or prison for more than 72 hours?	☐	☐	
In the past **three years** have you			
28. Been outside the United States or Canada?	☐	☐	
From **1980 through 1996**			
29. Did you spend time that adds up to three (3) months or more in the United Kingdom? (Review list of countries in the UK.)	☐	☐	
30. Were you a member of the US Military, a civilian military employee, or a dependent of a member of the US Military?	☐	☐	
From **1980 to the present**, did you			
31. Spend time that adds up to five (5) years or more in Europe? (Review list of countries in Europe.)	☐	☐	
32. Receive a blood transfusion in the United Kingdom or France? (Review list of countries in the UK.)	☐	☐	
From **1977 to the present**, have you			
33. Received money, drugs, or other payment for sex?	☐	☐	
34. Male donors: Had sexual contact with another male, even once? (Females: check "I am female.")	☐	☐	☐ I am female
Have you **EVER**			
35. Had a positive test for the HIV/AE virus?	☐	☐	
36. Used needles to take drugs, steroids, or anything not prescribed by your doctor?	☐	☐	
37. Used clotting factor concentrates?	☐	☐	
38. Had hepatitis?	☐	☐	

39. Had malaria?	☐	☐
40. Had Chagas' disease?	☐	☐
41. Had babesiosis?	☐	☐
42. Received a dura mater (or brain covering) graft?	☐	☐

Have you **EVER** (continued)	Yes	No
43. Had any type of cancer, including leukemia?	☐	☐
44. Had any problems with your heart or lungs?	☐	☐
45. Had a bleeding condition or a blood disease?	☐	☐
46. Had sexual contact with anyone who was born in or lived in Africa?	☐	☐
47. Been in Africa?	☐	☐
48. Have any of your relatives had Creutzfeldt-Jakob disease?	☐	☐

APPENDIX C. SAFETY REVIEW MEMO

FDP-1 PROTOCOL S-14-12 IND 17154
VERIFICATION OF INDIVIDUAL SUBJECT SAFETY REVIEW

To:	USAMRMC, Clinical Services Support Division	usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil
CC:	Westat	FDPWebSupport@westat.com
From:	Hoxworth Blood Center	Jose A. Cancelas, MD, PhD, Investigator

To ensure safety, an individual review of data is required for specific subjects as defined in the protocol.

This memo confirms completion of this review by both the Investigator and appointed Research Monitor, ~~Dr. Patricia Carey or~~ Dr. Matthew Montgomery.

Subject Identifier (SID): __ __ __ __ __ __

Infusion Date: __ __/ __ __/ __ __ __ __

Date Review Completed: __ __/ __ __/ __ __ __ __

- ☐ Physical Examination
- ☐ Vital Signs
- ☐ Medical History
- ☐ Laboratory Test Results

Results:

- ☐ *No safety issues or adverse events were identified.*
- ☐ *Safety issues or adverse events were identified during the review.*

Protocol-Defined Stopping Rules:

- ☐ *No protocol-defined Stopping Rules were met.*
- ☐ *One or more protocol-defined Stopping Rule was met.*

Details of safety issues were submitted following the protocol safety reporting procedures (Section 10.6).

Signature of Investigator:

_____

Jose A. Cancelas, MD, Phd **Date**

Signature of Research Monitor

_____

Matthew Montgomery, MD **Date**

NOTE: The original, signed version of this memo is maintained on-site at Hoxworth Blood Center as part of the subject's source documentation. An electronic copy will be included in the study's trial master file.

Version 3.0, November 16, 2017

APPENDIX D. TELEPHONE RECRUITMENT

Recruitment Telephone Call Script

"Hello_____. My name is_____and I am a staff member at Hoxworth Blood Center. I am reaching out to you regarding a research study that is looking for volunteers. You are being contacted because of your history of donating blood at our center and because you have expressed an interest in participating in research studies.

Would you be interested in learning more about our study today?"

- *If No:*
  - "Thank you for your time, we hope you continue to support Hoxworth Blood Center by donating blood in the future."
  - End the call and record response in the research participant database.
- *If Yes, but not a good time:*
  - "**Is there a better time to discuss the study with you? Would you like information about the study mailed to your house?**"
  - Arrange for a follow-up call at a later date, AND/OR
  - Collect information for mailing consent to the potential participant.
- *If Yes:*
  - "Thank you for your interest! Our study is looking at the safety of a new, experimental plasma product called freeze-dried plasma or FDP. Currently hospitals rely on infusions of fresh frozen plasma as definitive care for patients who are bleeding after major surgery or have been in an accident to help control bleeding, fight infection, and restore fluid levels. However, that type of plasma can take a couple of hours to thaw which can be life-threatening for patients who immediately need plasma products. A new method has been developed in which the plasma is 'freeze-dried' instead of frozen. FDP, like fresh frozen plasma, is made from donor plasma, but instead of being frozen it is changed to a powder form for storage through freeze-drying and can be rapidly dissolved back into a liquid form within a few minutes. Because FDP is an experimental product it is not currently approved by the FDA. Participants in the study will donate their own blood or plasma and will receive an infusion of their own reconstituted FDP. The amount of blood or plasma donated and infused depends on which study group you are assigned to. There are a lot of blood tests and some follow-up visits required of people who participate in the study."

I'd like to go over some pre-screening questions with you to see if you would be a good candidate for participation. Is that OK?

- *If Yes*:
  - "Great, let's get started."
  - Proceed to next question.
- *If No:*
  - "Thank you for taking the time to speak with me today."

Do you have any questions about the study so far?

- *If Yes:*
  - Answer all questions until the potential participant is satisfied.
  - Proceed to next question.
- *If No:*
  - Proceed to next question.

Are you currently participating in any other research studies?

- *If Yes:*
  - **Are you receiving an investigational product in the research study? When do you expect to complete that study?**
    - Record answers supplied by the potential participant to discuss with Dr. Cancelas. The exclusion criterion states that participants cannot have received an investigational agent within 1 month of infusion; but does not preclude participation entirely.
  - "Thank you, I'm not sure if you'll qualify for participation in this study but I'd like to go ahead and complete the rest of the pre-screening questions just in case you are eligible. I'll talk to Dr. Cancelas, the investigator for this study, about your responses."
  - Proceed to next question.
- *If No:*
  - Proceed to next question.

The expected duration of the study is approximately 4 months. Are you planning on remaining in the area (ex. Not moving out of state, etc.) during that time period?

- *If Yes:*
  - Proceed to next question.
- *If No:*
  - "Thank you for your time. Since there are several times throughout the study where you will need to come to Hoxworth Blood Center for tests, we are looking for participants who will be local to Hoxworth Blood Center for the duration of their time in the study."
  - End the call and record response in the research participant database.

Would you say your health is generally good?

- *If Yes*:
  - Proceed to next question.
- *If No:*
  - "Thank you for your time; unfortunately for the safety of the study participants we're only enrolling people who believe they are in good health. We hope you continue to support Hoxworth Blood Center donating blood in the future."

[For Females Only] **Are you pregnant, planning to get pregnant, or currently breastfeeding?**

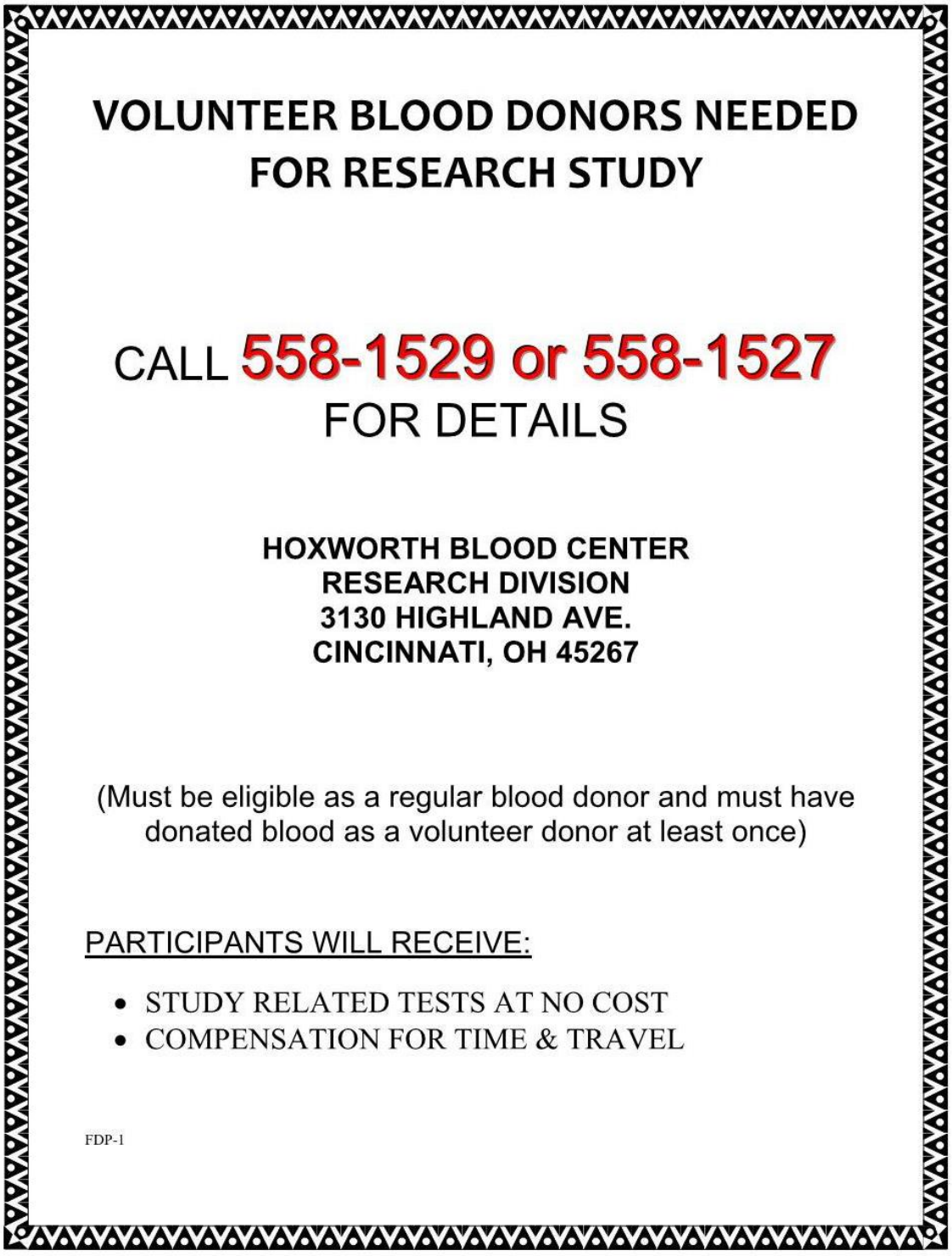
- *If Yes:*
  - "Thank you, unfortunately due to safety reasons we are only enrolling women who are not currently pregnant, planning on getting pregnant, or breastfeeding at this time. We hope you continue to support Hoxworth Blood Center donating blood in the future."
  - End the call and record response in the research participant database.
- *If No:*
  - Proceed to next question.

Are you interested in participating in this study?

- *If Yes:*
  - "I would like to set up an initial visit to go over the study in more depth. Attending this initial visit does not commit you to participating in the study. If you consent to participate by signing the informed consent form, you will be screened for all exclusion and inclusion criteria and we will collect blood and urine samples to confirm you are healthy enough to participate. We anticipate this visit could take up to 3 hours."
  - Schedule the consent and screening visit.
  - "Thank you for your interest in the study! Your initial visit is scheduled for _____. Please feel free to contact us if you have any questions about the study in the meantime. If you change your mind about participating in the study, or need to reschedule the screening visit, please contact us.
  - End the call and record response in the research participant database.
- *If No:*
  - "Thank you for taking the time to speak with me today. I really appreciate it."

If a printed copy of the Pre-Screening Telephone Call Script is used to document information collected during the call, then it must be maintained as part of the source documentation. If the subject signs a consent and is assigned a subject ID number (SID), then the paper copy of the Pre-Screening Telephone Call Script should be labeled with the SID.

APPENDIX E. RECRUITMENT FLYER



VOLUNTEER BLOOD DONORS NEEDED FOR RESEARCH STUDY

CALL **558-1529 or 558-1527**
FOR DETAILS

HOXWORTH BLOOD CENTER
RESEARCH DIVISION
3130 HIGHLAND AVE.
CINCINNATI, OH 45267

(Must be eligible as a regular blood donor and must have donated blood as a volunteer donor at least once)

PARTICIPANTS WILL RECEIVE:

- STUDY RELATED TESTS AT NO COST
- COMPENSATION FOR TIME & TRAVEL

FDP-1

APPENDIX F. DUKE ACTIVITY STATUS INDEX (DASI)

For each selection in the table, select either yes or no. If the answer is yes, the DSAI value corresponding to the question will be added to the total displayed at the bottom.

Item	Activity	Please Circle One		If Yes: DASI Value
1	Can you take care of yourself (eating, dressing, bathing, or using the toilet)?	**No**	**Yes**	2.75
2	Can you walk indoors such as around your house?	**No**	**Yes**	1.75
3	Can you walk a block or two on level ground?	**No**	**Yes**	2.75
4	Can you climb a flight of stairs or walk up a hill?	**No**	**Yes**	5.50
5	Can you run a short distance?	**No**	**Yes**	8.00
6	Can you do light work around the house like dusting or washing dishes?	**No**	**Yes**	2.70
7	Can you do moderate work around the house like vacuuming, sweeping floors, or carrying in groceries?	**No**	**Yes**	3.50
8	Can you do heavy work around the house like scrubbing floors or lifting and moving heavy furniture?	**No**	**Yes**	8.00
9	Can you do yard work like raking leaves, weeding, or pushing a power mower?	**No**	**Yes**	4.50
10	Can you have sexual relations?	**No**	**Yes**	5.25
11	Can you participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?	**No**	**Yes**	6.00
12	Can you participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?	**No**	**Yes**	7.50
		Total DASI:		

Assessment Done By:_____ Date: _____

APPENDIX G.IRON SUPPLEMENTATION FLYER

Freeze Dried Plasma (FDP) Research Study:
Iron Supplementation Information

Why am I receiving this information?

As a subject providing blood products for use in this study, we recommend the use of iron supplements. Iron supplements can be acquired over-the-counter and are taken to replace your body's iron that may be lost during the donation process.

Which iron supplement should I take?

Iron supplements come in several formulas and strengths. For subjects like you, we recommend the one packaged as:

☑ **27 mg of ferrous sulfate (free iron)**

How much should I take and when?

Take one tablet of the recommended iron once a day with your main meal of the day. By taking it with your main meal of the day, you will be less likely to experience any negative gastrointestinal effects.

How long do I need to take iron supplements for?

We generally recommend that you take the iron supplement, as described, for a minimum of 4 weeks after each blood product donation.

How will my iron levels be measured?

Before each donation, a hematocrit test to check your iron levels will be performed. If your hematocrit is too low you will not be able to give blood. If for some reason your iron levels continue to be low, we will recommend that you contact your Family Doctor. Your doctor may recommend that you take iron supplements for a longer period of time.

Jose A. Cancelas, MD, PhD
FDP Investigator
Research Division Director
Hoxworth Blood Center

IND #17154
Version 1.2, 2016 NOV 28

APPENDIX H.TELEPHONE FOLLOW-UP SCRIPT

Telephone Follow-Up Script

(Administered 48 and 72 hours and 14 days after each Infusion Visit, for subjects in all Cohorts.)

SID: _____

Introductory Telephone Script:

Hello,_____. This is_____from Hoxworth Blood Center following up after your last study visit. I would like to ask you some questions about any medical problems including any medications that you may have started taking since your last visit to the blood center.

A. Record the date, time, and visit information for the contact. This information will be recorded on the Telephone Follow-Up CRF.

Contact:	☐ 1st 48-Hour Call ☐ 2nd 48-Hour Call (Cohort 3) ☐ 1st 72-Hour Call ☐ 2nd 72-Hour Call (Cohort 3) ☐ 14-Day Call*
Date:	
Time:	

*For Cohort 3, the 14-Day Call only takes place after the second Infusion Visit.

B. **Review the following with the subject and record the responses on the checklist** provided below.

1. During the last 24 hours have you had any of the following:	**Response**		**Comment**
Headache or migraine?	☐ Yes	☐ No	
Any new vision or hearing defects?	☐ Yes	☐ No	
Loss of strength or sensitivity in any part of your body?	☐ Yes	☐ No	
Chest pain?	☐ Yes	☐ No	
Shortness of breath?	☐ Yes	☐ No	
Abdominal pain?	☐ Yes	☐ No	

Swollen legs, ankles, or calf pain?	☐ Yes	☐ No	
Rash or unusual bruising on your skin?	☐ Yes	☐ No	
Blood in your urine or stool?	☐ Yes	☐ No	
If the response to any question above is 'Yes', notify the Principal Investigator (PI) immediately. Reported signs and symptoms are recorded on the **Adverse Event CRF**.			
2. Are you currently taking any medications since the last visit?	☐ Yes	☐ No	
If yes, write down the name of each medication the subject is taking. Reported medications are recorded on the **Prior and Concomitant Medications CRF**.			

C. Confirm the subject's availability for upcoming study visit:
- *72-hour telephone contact (if calling for the 48-hour telephone contact);* ***OR***
- *7-day on-site visit (if calling for the 72-hour telephone contact).*

D. **Complete the Visit Report CRF to indicate the telephone contact took place. The Visit Report CRF is completed after each contact or visit.**

APPENDIX I. HEMOVIGILENCE FORM

FDP-1 Protocol Worksheet: Assessment of Transfusion-Related Adverse Events (TRAEs)

Adapted from the NHSN Hemovigilance Module Adverse Reaction Form

- This worksheet is to aid the Investigator in the initial assessment of all transfusion related adverse events. It is *not* a case report form.
- If a serious TRAE should occur, send a copy of this form to the USAMMDA Safety Office with the SAE Report Form to: usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil.
- Maintain the originals of completed forms at the site as source documentation.

Site: Hoxworth Blood Center **IND #:** 17154

SUBJECT INFORMATION

Subject Identification (SID) #: _____			Date of Birth: __ __/__ __/__ __ __ __
Gender:	☐ M ☐ F ☐ Other	Study Cohort: ☐ 1 ☐ 2 ☐ 3	
Last Name:		First Name:	
Blood Group:	☐ A- ☐ A+ ☐ B- ☐ B+ ☐ AB- ☐ AB+ ☐ O- ☐ O+ ☐ Type/Crossmatch not performed		

EVENT/REACTION DETAILS

Transfusion-Related Adverse Event (Diagnosis): _____

Date reaction occurred: __ __/__ __/__ __

Time reaction occurred: __ __:__ __ (HH:MM) ☐ Time unknown

Signs and symptoms, laboratory: (CHECK ALL THAT APPLY)

Cardiovascular:	**Cutaneous:**	**Pain:**
☐ Blood pressure decrease	☐ Edema	☐ Abdominal pain
☐ Shock	☐ Flushing	☐ Back pain
Hemolysis/Hemorrhage:	☐ Jaundice	☐ Flank pain
☐ Disseminated intravascular coagulation	☐ Other rash	☐ Infusion site pain
☐ Hemoglobinemia	☐ Pruritus (itching)	**Respiratory:**
☐ Positive antibody screen	☐ Urticaria (hives)	☐ Bilateral infiltrates on chest x-ray
Generalized:	**Renal:**	☐ Bronchospasm
☐ Chills/rigors	☐ Hematuria	☐ Cough
☐ Fever	☐ Hemoglobinuria	☐ Hypoxemia
☐ Nausea/vomiting	☐ Oliguria	☐ Shortness of breath
☐ Other: (specify)		

Continue to page 2→

CDC 57.304 Rev. 5, v8.5
FDP1, V1.0

Page 1 of 4

Site: Hoxworth Blood Center
IND #: 17154

SID#: _____

INVESTIGATION RESULTS

(Use case definition criteria in NHSN protocol.)

Adverse reaction: (*CHECK ONE*)

- ☐ Allergic reaction, including anaphylaxis
- ☐ Acute hemolytic transfusion reaction (AHTR)
  - ☐ Immune Antibody: _____
  - ☐ Non-immune (specify) _____
- ☐ Delayed hemolytic transfusion reaction (DHTR)
  - ☐ Immune Antibody: _____
  - ☐ Non-immune (specify) _____
- ☐ Delayed serologic transfusion reaction (DSTR) Antibody(ies): ____ ____ ____ ____ ____ ____
- ☐ Febrile non-hemolytic transfusion reaction (FNHTR)
- ☐ Hypotensive transfusion reaction
- ☐ Infection

  Was a test performed on the unit post-transfusion to detect a specific pathogen? (i.e., culture, serology, NAT)

  ☐ Yes ☐ No If Yes, positive or reactive results? ☐ Yes ☐ No

  Org1 _____ Org2 _____ Org3 _____
- ☐ Post transfusion purpura (PTP)
- ☐ Transfusion associated circulatory overload (TACO)
- ☐ Transfusion associated dyspnea (TAD)
- ☐ Transfusion associated graft vs. host disease (TA-GVHD)

  Did patient receive non-irradiated blood product(s) in the two months preceding the reaction? ☐ Yes ☐ No
- ☐ Transfusion related acute lung injury (TRALI)

Antibody studies performed: (*OPTIONAL*)

	Not Performed	Negative	Test result positive		
			Cognate or cross reacting antigen present	No cognate or cross reacting antigen present	Not tested for cognate antigen
Donor or unit HLA specificity	☐	☐	☐	☐	☐
Donor or unit HNA specificity	☐	☐	☐	☐	☐
Recipient HLA specificity	☐	☐	☐	☐	☐
Recipient HNA specificity	☐	☐	☐	☐	☐

- ☐ Unknown
- ☐ Other (*SPECIFY*) _____

Case definition criteria: ☐ Definitive ☐ Probable ☐ Possible ☐ N/A

Site: Hoxworth Blood Center
IND #: 17154

SID#: _____

:

SEVERITY	*On AE CRF and SAE Report Form, report using the indicated toxicity grade equivalent.*	Relatedness	
☐ Non-severe	GRADE 1 OR 2	☐ Definite	
☐ Severe	GRADE 3	☐ Probable	
☐ Life-threatening	GRADE 4	☐ Possible	
☐ Death	GRADE 5	☐ Doubtful	
		☐ Ruled Out	
		☐ Not determined	

OUTCOME

Outcome: ☐ Death* ☐ Major or long-term sequelae ☐ Minor or no sequelae ☐ Not determined

Date of Death: __ __/__ __/__ __ __ __ *Report deaths per FDP-1 MOP.

→*IF **DEATH***, relationship of death to transfusion:

☐ Definite ☐ Probable ☐ Possible ☐ Doubtful ☐ Ruled Out ☐ Not determined

UNIT DETAILS

For the adverse reaction/event, were investigational unit(s) implicated (i.e., responsible for)? ☐ Yes ☐ No ☐ N/A

→*IF **YES**, COMPLETE THE INFORMATION BELOW.*

Transfusion **End** Date/Time: ___/___/_____ (MM/DD/YY) ___ ___:___ ___ (TIME)

Total number of units infused: _____ (# UNITS)

UID #	UNIT EXPIRATION	UNIT'S BLOOD GROUP
	___/___/_____MM/DD/YY ___ ___:___ ___ HH:MM	☐ A- ☐ A+ ☐ B- ☐ B+ ☐ AB- ☐ AB+ ☐ O- ☐ O+
	___/___/_____MM/DD/YY ___ ___:___ ___ HH:MM	☐ A- ☐ A+ ☐ B- ☐ B+ ☐ AB- ☐ AB+ ☐ O- ☐ O+
	___/___/_____MM/DD/YY ___ ___:___ ___ HH:MM	☐ A- ☐ A+ ☐ B- ☐ B+ ☐ AB- ☐ AB+ ☐ O- ☐ O+

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FDP1, V1.0

Site: Hoxworth Blood Center
IND #: 17154

SID#: _____

INVESTIGATOR SIGNATURE

_____
Name of Investigator

_____
Signature

_____
Date (MM/DD/YY)

APPENDIX J. SAE FORM

US Army Medical Materiel Development Activity

Serious Adverse Event (SAE) Report Form

- Submit form to: usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil according to the protocol's SAE reporting procedures described in Chapter 9 of the Manual of Operations.
- Retain originals of all information provided to USAMRMC/USAMMDA in the Site Investigator File.
- **Ensure the information displayed in the table directly below appears at the top of each page (e.g., subject identification (SID) number, protocol numbers (IND and S number), study site name, and country).**

Sponsor: The Surgeon General, Department of the Army	**Protocol IND #: 17154**	**Protocol S #: S-14-12 (FDP-1)**
Study Country: **USA**	**Study Site:** **Hoxworth Blood Center**	**Subject Number:** ___ ___ ___ ___ ___ ___

☐ **Initial Report/Date** ____/_____/_____	☐ **Follow-up Report/Date** ____/_____/_____	**Date Investigator Aware of Event** ____/_____/_____
Study Type: ☐ Open-Label ☐ Single-Blind ☐ Double-Blind ☐ Other: _____		**Study Blind Broken?** ☐ Yes ☐ No ☐ N/A

A. SUBJECT INFORMATION

Date of Birth ____/_____/_____	Race/Ethnicity (per Demographic CRF):	Height: _____ cm _____in	Weight: _____kg _____LB

Is this SAE associated with pregnancy? ☐ No ☐ Unknown ☐ Yes (submit pregnancy report form)	Gender: ☐ Male ☐ Female

B. SERIOUS ADVERSE EVENT (SAE)

SAE Term: (diagnosis; if unavailable, primary symptom)	**Onset Date:** (date event met serious criteria; DD/MMM/YYYY)	**Resolution Date:** (DD/MMM/YYYY)

Has SAE term changed since the prior report?
☐ Yes ☐ No ☐ N/A **Previous SAE Term:** **Updated SAE Term:**

Regulatory Serious Criteria: *(indicate all that have a Yes response)*

☐ Is the adverse event associated with a congenital abnormality or birth defect?

☐ Did the adverse event result in persistent or significant disability or incapacity?

☐ Did the adverse event result in death?

☐ Did the adverse event result in initial or prolonged hospitalization for the subject?

Admission Date: _____ Discharge Date: _____

☐ Is the adverse event life threatening?

☐ Is the adverse event a medically important event* not covered by other "serious" criteria? *(*An important medical event is one that, based upon appropriate medical judgement, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes.)*

Severity (Toxicity Grade): Record the most severe intensity of the event.

☐ Grade 1 – Mild; Does not interfere with routine activities; minimal level of discomfort.

☐ Grade 2 – Moderate; Interferes with routine activities; moderate level of discomfort.

☐ Grade 3 – Severe; Unable to perform routine activities; significant level of discomfort.

☐ Grade 4 – Potentially Life Threatening; event indicates hospital or emergency room visit.

☐ Grade 5 – Fatal; results in death.

US Army Medical Materiel Development Activity

Serious Adverse Event (SAE) Report Form

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Sponsor: The Surgeon General, Department of the Army	**Protocol IND #: 17154**	**Protocol S #: S-14-12 (FDP-1)**
Study Country: **USA**	**Study Site:** **Hoxworth Blood Center**	**Subject Number:** ___ ___ ___ ___ ___ ___

Outcome of Event: Describe the status of the subject when the event ended by indicating one of the following categories:

☐ Not Recovered/Not Resolved – The subject has not yet returned to his/her previous health status, continues to be followed for the adverse event. This category also includes adverse events present at the time of death but which did not specifically result in the subject's death.

☐ Recovered/Resolved – The subject returned to his/her previous health status with no subsequent problems.

☐ Recovering/Resolving – The subject is recovering; the event is resolving.

☐ Recovered/Resolved with Sequelae – The subject has a change in health status subsequent to the adverse event. Sequela, as long as this does not constitute such impairment, does not fulfil the criteria for a "disabling" event. (**Specify sequelae)** _____

☐ Fatal – The subject died. For the specific event(s) that resulted in death, indicate the date of death as the end date of the event(s).

☐ Unknown

Suspect Investigational Product (IP) Relationship/Causality: Medical judgement should be used to determine the relationship, including kind and pattern of reaction, temporal relationship, subject's clinical status, co-medication, etc.

Select one of the following; provide a rationale in section 1 or 2 below, as applicable.

☐ **Not Related** (complete section 1)	No relationship to investigational product. Applies to those events for which evidence exists that there is an alternate etiology. **Provide the alternate etiology:** _____
☐ **Unlikely** (complete section 1)	Likely unrelated to the investigational product. Likely to be related to factors other than the investigational Product, but cannot be ruled out with certainty.
☐ **Possible** (complete section 2)	An association between the event and administration of investigational product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology such as the subjec clinical status or underlying factors including other therapy.
☐ **Probable** (complete section 2)	There is a high degree of certainty that a relationship to the investigational product exists. There is a reasonable temporal association, and the event cannot be explained by known characteristics of the subject' clinical state or factors including other therapy.
☐ **Definite** (complete section 2)	An association exists between the receipt of investigational product and the event. An association to other factors has been ruled out.

1. Rationale for Not Related/Unlikely Related Assessment
(Check all that apply):

☐ Event attributed to concomitant medication or disease
☐ Event not reasonably temporally associated with IP administration
☐ Event is expected in targeted disease and/or population
☐ Negative de-challenge
☐ Negative re-challenge
☐ Other (specify): _____

2. Rationale for Possibly/Probably/Definitely Related Assessment
(Check all that apply):

☐ Temporal relationship of event to IP exposure
☐ Event is known to be associated with the IP or IP class
☐ Event improved on discontinuation or dose reduction of IP
☐ Event reoccurred on rechallenge with IP
☐ Biological plausibility
☐ Other (specify): _____

US Army Medical Materiel Development Activity

Serious Adverse Event (SAE) Report Form

- Submit form to: usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil according to the protocol's SAE reporting procedures described in Chapter 9 of the Manual of Operations.
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Sponsor: The Surgeon General, Department of the Army	**Protocol IND #: 17154**	**Protocol S #: S-14-12 (FDP-1)**
Study Country: **USA**	**Study Site:** **Hoxworth Blood Center**	**Subject Number:** ___ ___ ___ ___ ___ ___

C. INVESTIGATIONAL PRODUCT (IP) *(Add additional rows if applicable – right click, insert row)*

IP Name	Dose Number (1, 2, 3, etc.)	IP Start Date(s) (DD/MMM/YYYY)	IP Stop Date(s) (DD/MMM/YYYY)	Total Dose (include units)	IP Route

Action taken with the IP: (record dates as: DD/MMM/YYYY)

☐ Dose increased Date increased:

☐ Dose not changed

☐ Dose reduced Date reduced:

☐ Drug interrupted Stop date: Date restarted:

☐ Drug withdrawn Stop date:

☐ Not applicable (provide justification):

☐ Unknown

Event abated after IP stopped (dechallenge)/or dose reduced: ☐ Y ☐ N ☐ N/A ☐ Unknown

Event reappeared after reintroduction (rechallenge) of IP: ☐ Y ☐ N ☐ N/A ☐ Unknown

D. CONCOMITANT MEDICATION(S) *(within 30 days of SAE onset or per protocol) If the eCRF is provided (preferable), do not complete this section. (Add additional rows if applicable – right click, insert row)*

Drug Name (Generic Preferred)	Dose	Route	Frequency	Suspect Drug	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)
				☐ Y ☐ N		
				☐ Y ☐ N		
				☐ Y ☐ N		
				☐ Y ☐ N		
				☐ Y ☐ N		

US Army Medical Materiel Development Activity

Serious Adverse Event (SAE) Report Form

- Submit form to: usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil according to the protocol's SAE reporting procedures described in Chapter 9 of the Manual of Operations.
- Retain originals of all information provided to USAMRMC/USAMMDA in the Site Investigator File.
- **Ensure the information displayed in the table directly below appears at the top of each page (e.g., subject identification (SID) number, protocol numbers (IND and S number), study site name, and country).**

Sponsor: The Surgeon General, Department of the Army	**Protocol IND #: 17154**	**Protocol S #: S-14-12 (FDP-1)**
Study Country: **USA**	**Study Site:** **Hoxworth Blood Center**	**Subject Number:** ___ ___ ___ ___ ___ ___

E. DESCRIBE EVENT(S) *(Chronological summary of signs and symptoms, vital signs, diagnosis, treatment, outcome and autopsy details [if applicable]). Expand row as needed.*

F. RELEVANT LABORATORY TESTS *(If the e-CRF or lab reports are provided [preferable], do not complete this section.) Add additional rows as needed – right click, insert row.*

Laboratory Test (Relevant to SAE Only)	**Date of Test** (DD/MMM/YYYY	**Normal Ranges** (Include Units)	**Results** (Include Units)	**Baseline** (Include Units)

G. RELEVANT MEDICAL HISTORY *(Provide relevant medical history, including pre-existing medical conditions. If the e-CRF is provided [preferable], do not complete this section.)*

Diagnosis	**Start date** (DD/MMM/YYYY)	**Stop date** (DD/MMM/YYYY)	**Ongoing:**
			☐ Y ☐ N
			☐ Y ☐ N
			☐ Y ☐ N
			☐ Y ☐ N
			☐ Y ☐ N

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Sponsor: The Surgeon General, Department of the Army	**Protocol IND #: 17154**	**Protocol S #: S-14-12 (FDP-1)**
Study Country: **USA**	**Study Site:** **Hoxworth Blood Center**	**Subject Number:** ___ ___ ___ ___ ___ ___

H. DEATH INFORMATION

Date of Death: _____ (DD/MMM/YYYY) Cause of Death: _____

Death certificate completed? ☐ Yes (attach copy) ☐ No ☐ Pending

Autopsy performed? ☐ Yes (attach copy) ☐ No ☐ Pending

I. COMPLETED BY:

Name: **Title:** **Date:** ____/____/____ (DD/MMM/YYYY)

J. INVESTIGATOR SIGNATURE/DATE: *(Signature Required)*

Name: **Title:** **Date:** ____/____/____ (DD/MMM/YYYY)

APPENDIX K.PREGNANCY FORM

US Army Medical Materiel Development Activity

Pregnancy Report Form

- Record all dates in the DAY/MONTH/YEAR (DD/MMM/YYYY) format.
- **Complete Study Country, Study Site, and Subject Number and ensure all pages contain the protocol/site/subject information in the table below.**
- Submit form to: usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil (Refer to the protocol for pregnancy reporting time lines/requirements and alternate notification information).
- Retain originals of all information faxed to USAMRMC/USAMMDA in the Investigator Site File.

Sponsor: The Surgeon General, Department Of the Army (TSG-DA)	Protocol IND #: 17154	Protocol S #: S-14-12
Study Country:	Study Site:	Subject Number:

☐ INITIAL ☐ FINAL ☐ TRIMESTER UPDATE **(Only complete Subject Number above and sections A and H unless additional information becomes available.)**

A. SUBJECT DEMOGRAPHICS/ETHNICITY

Date of Birth: ___/____/_____	Age:	Weight: _____ kg _____ lb	Height: _____ cm _____ in

☐ Asian ☐ Black/African American ☐ Latino/ Hispanic ☐ Native American ☐ Pacific Islander ☐ White ☐ Unknown ☐ Other

B. PREGNANCY INFORMATION

Date Pregnancy First Reported to Site: ___/____/_____	Screening Pregnancy Test Date: ___/____/_____	Negative Screening Pregnancy Test? ☐ Yes ☐ No
Date Pregnancy Confirmed: ___/____/_____ ☐ Urine Test ☐ Serum Test	Date of Last Menstrual Period: ___/____/_____	Estimated Delivery Date: ___/____/_____

C. REPRODUCTIVE and MEDICAL HISTORY

Gravida (Total # of Prior Pregnancies): Para (Total # of Prior Live Births):	Abortions (Total # of Terminations): Spontaneous: Elective:	☐ Unknown

Relevant Medical History:

D. CONCOMITANT MEDICATIONS *(If a copy of the Case Report Form [eCRF] page is provided [preferable], do not complete this section.)* Add additional rows if applicable.

Drug Name (Generic preferred)	Dose (include units)	Route	Frequency	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)

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Sponsor: The Surgeon General, Department Of the Army (TSG-DA)	Protocol IND #: 17154	Protocol S #: S-14-12
Study Country:	Study Site:	Subject Number:

E. STUDY DRUG *(If a copy of the Case Report Form [eCRF] page is provided [preferable], do not complete this section.)*

First Dose Date: ___/____/_____ **Last Dose Date:** ___/____/_____ **# of Doses:** _____

SUSPECT STUDY DRUG RELATIONSHIP/CAUSALITY:

☐ Not Related ☐ Unlikely Related ☐ Possibly Related ☐ Probably Related ☐ Definitely Related

ACTION TAKEN WITH THE INVESTIGATIONAL PRODUCT:

☐ No Action Taken (Dose Not Changed)
☐ Stopped Temporarily - Stop Date: ___/____/_____ Restart Date: ___/____/_____
☐ Unknown ☐ Not Applicable ☐ Permanently Discontinued/Withdrawn: Stop Date: ___/____/_____

F. METHOD OF BIRTH CONTROL *(Check **all** methods in use since starting study drug.)*

☐ Abstinence	☐ Intrauterine Device (IUD)	☐ Sterilization (Female)
☐ Condom	☐ Oral Contraceptive	☐ Sterilization (Male)
☐ Diaphragm	☐ Rhythm Method	☐ None
☐ Injection/Implant: _____	☐ Spermicide	☐ Other: _____

Reason for Contraceptive Failure:

G. SUMMARY OF DIAGNOSTIC TESTS PERFORMED TO DATE (i.e., ultrasound, amniocentesis)

# of Fetuses: _____

H. TRIMESTER UPDATES

First Trimester Update:	Second Trimester Update:	Third Trimester Update:
☐ No Complications	☐ No Complications	☐ No Complications
☐ Other (*provide details*):	☐ Other (*provide details*):	☐ Other (*provide details*):

I. COMPLICATIONS WITH PREGNANCY TO DATE

☐ None ☐ Yes (*provide comments below*):

Sponsor: The Surgeon General, Department Of the Army (TSG-DA)	Protocol IND #: 17154	Protocol S #: S-14-12
Study Country:	Study Site:	Subject Number:

J. TERMINATION	K. DELIVERY
☐ Elective ☐ Spontaneous Abortion ☐ Ectopic Date of Termination: ___/____/_____	☐ Vaginal Birth ☐ C-Section: ☐ Scheduled ☐ Emergency Date of Delivery: ___/____/_____

L. BIRTH TYPE

☐ Premature Birth/Healthy Infant
☐ Term Birth/Healthy Infant
☐ Term Birth/Congenital Anomaly*
☐ Stillborn
☐ Premature Birth/Congenital Anomaly*

*If Anomaly, Provide Comments Below:

M. NEONATE OUTCOME

Gender	Birth Weight	Head Circumference	Length	Gestational Age at Delivery	APGAR Scores		
					#1	#2	#3
☐ Male ☐ Female							

N. COMMENTS

O. COMPLETED BY:

Name:	Title:	Date:

P. INVESTIGATOR SIGNATURE/DATE:

	Date: