A Pilot Trial of Using Pre-Transplant Risk Stratification and Prophylactic Defibrotide to Prevent Serious Thrombotic Microangiopathy in High-Risk Hematopoietic Stem Cell Transplant Patients

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Protocol Signature Page

Protocol No.: **Version Date:**

1. I agree to follow this protocol version as approved by the UCSF Committee on Human Research (CHR)
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

Participating Site(s)

Telephone:	Telephone:	Telephone:
E-mail:	E-mail:	E-mail:

Principal Investigator **Site**

_____ _____
Printed Name

_____ _____
Signature Date

Abstract

Title	A Pilot Trial of Using Pre-Transplant Risk Stratification and Prophylactic Defibrotide to Prevent Serious Thrombotic Microangiopathy in High-Risk Hematopoietic Stem Cell Transplant Patients
Patient population	Pediatric patients age 0-30 years receiving autologous or allogeneic HSCT meeting TMA high risk criteria.
Rationale for Study	TMA is a common complication in the stem cell transplant population. Certain populations within the HSCT population are at a higher risk than others. Defibrotide is an endothelial stabilizing agent which may prevent the endothelial damage that triggers TMA in HSCT patients. The feasibility, safety, and efficacy of defibrotide prophylaxis in a pediatric transplant population is unknown.
Primary Objective	To determine the feasibility and safety of defibrotide in children receiving HSCT.
Secondary Objectives	To determine the efficacy of defibrotide prophylaxis in preventing severe TMA in pediatric patients receiving HSCT.
Study Design	Single arm non-randomized Phase II safety and feasibility trial of un-blinded defibrotide prophylaxis.
Number of patients	25
Duration of Therapy	Patients may continue treatment for 28-35 days from time of study drug initiation.
Duration of Follow up	Follow up for 6 months post-HSCT per HSCT standard of care.
Duration of study	The study will reach completion 30 months from the time the study opens to accrual.
Study Drugs	Defibrotide 6.25mg/kg IV Q6h for 28-35 days.
Safety Assessments	Weekly inpatient assessments of administration feasibility, hypersensitivity reaction, and bleeding while defibrotide is administered. This includes all HSCT SOC evaluations including routine clinical evaluations and laboratory assessments.
Efficacy Assessments	Efficacy will be based on overall incidence of TMA as well as incidence of severe TMA within 6 months post-HSCT, as defined in the protocol.

Unique Aspects of this Study	This is the first study to evaluate safety and efficacy of defibrotide in pediatric patients for prevention of severe TMA.

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANG-2	angiopoietin 2
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
BCH-SF	Benioff Children's Hospital- San Francisco
BMT	bone marrow transplant
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CH50	complement activity
CHR	Committee on Human Research (UCSF IRB)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose limiting toxicity
DSMP	Data and Safety Monitoring Plan
FCBP	female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCT	hematocrit
HSCT	hematopoietic stem cell transplant
HCV	hepatitis C virus
HGB	hemoglobin
HIV	human immunodeficiency virus

List of Abbreviations

ICH	International Conference on Harmonization
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
PAI-1	plasminogen activator inhibitor – 1
PD	disease progression
PK	pharmacokinetics
PO	*per os* (by mouth, orally)
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRC	Protocol Review Committee (UCSF)
PT	prothrombin time
PTT	partial thromboplastin time
QOL	Quality of Life
RBC	red blood cell (count)
SAE	serious adverse event
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ST2	suppression of tumorigeneicity
TBI	total body irradiation
TMA	thrombotic microangiopathy
TRM	treatment related mortality
ULN	upper limit of normal
WBC	white blood cell (count)

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1 Introduction

1.1 Background on Indication

Hematopoietic stem cell transplant (HSCT) is associated with an appreciable degree of transplant-related (i.e. toxic) mortality (TRM). The incidence of TRM at 1-year post-HSCT ranges from 5-15% depending upon the stem cell source utilized (Wingard, J Clin Oncol 2011). The UCSF BCH-SF BMT program has reviewed all cases of non-relapse related death from 2012-2015 and identified a complication of endothelial injury known as transplant associated thrombotic microangiopathy (TMA) as the most common cause of TRM in our patient population.

TMA is a multi-system disease in which widespread endothelial injury leads to microangiopathic hemolytic anemia, intravascular platelet activation and formation of thrombi within the microcirculation. The endolethial injury then promotes the complement cascade leading to additional injury to the endothelium further propagating the disorder.

TMA predominantly occurs in the kidneys but can affect the liver, lungs, intestines and brain. The risk factors for the development of TMA include myeloablative and reduced intensity conditioning regimens, calcineurin inhibitors (tacrolimus, cyclosporine), mTOR inhibitors (sirolimus), and infections. Additional risk factors include mismatched donors, ABO mismatch, and non-Caucasian patients. When genetic testing was performed looking at seventeen genes involved in the pathogenesis of other thrombotic microangiopathies, non-Caucasian patients with TMA were found to have more genetic variations when compared Caucasian patients (Jodele, Blood 2016).

Diagnosis of TMA can be difficult as systemic signs and symptoms of TMA are often similar to other common transplant complications, such as medication induced hypertension and cytopenias. Unlike in thrombocytopenic purpura, patients with TMA have normal ADAMTS13 activity. A renal biopsy would be useful in diagnosis however is often not possible given the risk factors of the procedure in a transplant patient.

The reported prevalence of TMA is varied likely due to diagnostic uncertainty and center expertise, but large retrospective studies have reported it as 10-39%, with the majority of cases occurring in the first 100 days after transplant. Of the patients who develop TMA, approximately half of them will develop severe disease. Outcomes are poor with a reported 30-50% mortality rate and as high as 80% in patients with severe disease. Furthermore, survivors of TMA may have significant morbidity (e.g. renal failure and need for long-term dialysis, heart failure, and significantly prolonged hospital admission).

There is no gold standard of treatment for TMA. Supportive care including renal support, discontinuation of calcineurin inhibitors and treatment of infections. Treatment options include plasma exchange, complement cascade blockade, and defibrotide. Early treatment is crucial to decrease morbidity and mortality.

Interestingly, our most severe cases of TMA have occurred in patients NOT receiving calcineurin inhibitors or sirolimus. Despite the early recognition and treatment of TMA, we have continued to see poor outcomes treating with complement blockade alone. This suggests that complement activation may trigger a complex cascade of parallel inflammatory mediators that lead to end organ damage independent of the complement pathway. Therefore, our goal is to prevent TMA whenever possible via augmentation of endothelial repair.

1.2 Background on the Compounds

Refer to the Investigator's Brochure/approved labeling for detailed background information on defibrotide.

1.3 Rationale for the Proposed Study

Upon retrospective review of our cases of TMA and the medical literature, we are now classifying patients as either standard-risk for the development of TMA, or high-risk, based on the following clinical criteria:

1. Patients undergoing tandem autologous transplant with thiotepa in one or more of the conditioning regimens.

OR:

2. Patients with at least 3 of the following characteristics:
   a) >10 years of age
   b) Non-Caucasian race/ Hispanic ethnicity
   c) Undergoing haploidentical transplant
   d) Minor ABO Mismatch

Using these criteria, we retrospectively reviewed 160 transplants performed from 1/1/13 to 9/30/16. There were 13 cases of TMA total (8.1%), with 7 cases (4.4%) deemed severe by the onset of renal failure, development of pericardial effusion, and/or death. In the 138 standard-risk patients, there were 6 total cases of TMA, but only 1 was severe (0.7%). Conversely, in the 22 high-risk patients there were 7 total TMA cases, 6 of which were severe (27.3%). Most cases showed evidence of evolving TMA before Day +100 post-HCT, and some cases of TMA were evident within a week following HCT.

Several groups have demonstrated that the onset of endothelial injury and clinical TMA typically begins within 4-6 weeks following HCT (Jodele Blood Rev 2015, Obut BMT 2016). Therefore, the hypothesis is that in high-risk patients the administration of certain combinations of high-dose conditioning agents (radiation and/or chemotherapy) and/or post-HSCT inflammatory events initiate the complement pathway to aberrantly attack the endothelium. Although the current standard treatment for post-transplant microangiopathic processes involves targeting inflammatory mediators with complement blockade and plasmapheresis, these therapies do not address the prevention or treatment of the initial pathologic trigger, namely, endothelial damage.

Defibrotide is an anticoagulant and fibrinolytic agent that has been shown to be an effective treatment in other endothelial disorders such as hepatic veno-occlusive disease (Richardson Blood 2002). It is a polydeoxyribonucleotide salt that blocks plasminogen activator inhibitor-1 (PAI-1) and attenuates the effect of tumor necrosis factor. It also increases prostaglandin E2 and prostacyclin levels which alters the platelet activity adhesion and aggregation and relaxes the smooth muscle of blood vessel walls. All of this likely protects the endothelium from damage. Yeates et al have shown that patients with TMA who were treated with defibrotide had a 77% response rate. (Yeates et al, Bone Marrow Transplantation, 2017).

The use of defibrotide in the context of VOD treatment and prevention has been studied extensively. A landmark report showed that defibrotide given to children during stem cell

transplant conditioning is safe and effective in the prevention of veno-occlusive disease and, incidentally, acute graft-versus-host disease (Corbacioglu, Lancet 2012). However, there has not been a prospective study to show that such prophylaxis is effective in the prevention of TMA.

1.4 Correlative Studies

Biomarkers indicative of endothelial damage and TMA activity will be drawn to assess subclinical TMA activity as well as risk for subsequent development of TMA while on defibrotide. These include plasma free hemoglobin (UCSF clinical lab), suppression of tumorigeneicity (ST2, Viracor), angiopoietin 2 (Ang2, Myriad), and plasminogen activator inhibitor – 1 (PAI-1, Quest). Study labs will be assessed at 4 time points prior to Day +21, and at diagnosis of TMA.

Hypothesis:

1. The incidence of TMA will correlate with increases in one or more of these biomarkers over baseline at any time post-HSCT.

2. The severity of TMA will correlate with a maximum increase in one or more of these biomarkers.

This will provide a predictive basis for future patients who may require preemptive treatment of early / preclinical TMA.

2 Objectives of the Study

2.1 Primary

- To determine the safety and feasibility of administering prophylactic Defibrotide (provided by Jazz Pharmaceuticals) to a pilot population of patients at clinical high-risk for the development of severe TMA following HSCT. Safety to be determined with regard to bleeding risk and risk of hypersensitivity reaction. Feasibility to be determined with regard to administration concurrently with chemotherapy and supportive medications before, during, and after stem cell infusion

2.2 Secondary

- To determine if administration of prophylactic Defibrotide will prevent the development of TMA in clinically high-risk patients compared to historic controls.
    - Incidence of TMA in the first 6 months post-HSCT will be compared to incidence in a similar cohort of historical controls.
    - Incidence of severe TMA as defined by any TMA with the following complications:
        - Renal dysfunction requiring dialysis
        - Pleural or pericardial effusion requiring any medical or surgical intervention
        - CNS dysfunction including seizure, PRES
        - Death

2.3 Exploratory Objectives, Other Assessments

- Biomarker specimens will be drawn at 4 time points prior to development of TMA. Values will be analyzed to determine whether any one biomarker or a combination of biomarkers may be predictive of TMA development or severity.

2.4 Endpoints

2.4.1 Primary Endpoints

- Incidence of missed doses of defibrotide
- Incidence of reportable SAE's
- Incidence of clinically significant bleeding requiring discontinuation of therapy
- Incidence of hypersensitivity reaction requiring discontinuation of therapy

2.4.2 Secondary Endpoints

- Incidence of TMA as diagnosed by criteria listed in section 7.2.1.
- Incidence of severe TMA as diagnosed by criteria listed in 7.2.2.

2.4.3 Exploratory Endpoints

- Incidence of elevation of single or combination of biomarkers predictive of development of TMA

3 Study Design

3.1 Characteristics

This is an open-label, single arm pilot study of defibrotide given as prophylaxis to patients receiving a conditioned stem cell transplant for the purpose of preventing post-transplant microangiopathy.

3.2 Number of Subjects

25 patients are expected to be enrolled.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, each patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Age 0-30 years of age
2. Life expectancy > 6 months
3. ECOG or Karnofsky Performance Status >40
4. Meets minimum organ function requirements per institutional SOC guiding clearance for autologous or allogeneic stem cell transplantation.
5. Patients must meet TMA High-Risk criteria

    A. Patients undergoing tandem autologous transplant with thiotepa in one or more of the conditioning regimens.

OR:

    B. . Patients with at least 3 of the following characteristics:
        a. >10 years of age
        b. Non-Caucasian race/ Hispanic ethnicity
        c. Undergoing haploidentical transplant
        d. Minor ABO Mismatch

6. The effects of defibrotide on the developing human fetus are unknown. For this reason and because other therapeutic drugs used as a part of transplant are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception: abstinence per institutional stem cell transplantation guidelines, for the duration of study participation and for a minimum of 2 weeks after last dose of study drug. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 2 weeks after last dose of study drug.
7. Ability to understand a written informed consent document, and the willingness to sign it

3.3.2 Exclusion Criteria

1. Age >30 years
2. Life expectancy < 6 months
3. Known bleeding diathesis or bleeding risk deemed by the treating physician to be a contraindication to administration of anticoagulants.
4. Known hypersensitivity reaction to defibrotide
5. Any patient not meeting TMA High-Risk criteria as defined in section 1.3
6. Pregnant women are excluded from this study because they will be receiving teratogenic therapy as part of the stem cell transplant.

3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment should begin the day prior to initiation of conditioning and continue until Day +21 post-HSCT, or:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.

3.5 Duration of Follow Up

Patients will be followed for 6 months post-HSCT, or until death, whichever occurs first. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment-related adverse events to Grade 2 or lower.

3.6 Study Timeline

Accrual is estimated to begin in Fall 2017 and continue through Fall 2019. Patients will be followed for safety and efficacy through Spring 2020.

3.6.1 Primary Completion

The study will reach primary completion 24 months from the time the study opens to accrual.

3.6.2 Study Completion

The study will reach study completion 30 months from the time the study opens to accrual.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Investigational Drug #1

Defibrotide is available as a solution, Intravenous, as sodium [preservative free]: Defitelio: 200 mg/2.5 mL (2.5 mL). Refer to the package insert for complete information.

Classification:
Therapeutic Category: Antiplatelet Agent; Thrombolytic Agent

Mechanism of Action:
Defibrotide augments plasmin enzymatic activity to hydrolyze fibrin clots. It reduces endothelial cell (EC) activation and increases EC-mediated fibrinolysis by increasing tissue plasminogen activator and thrombomodulin expression, as well as by decreasing von Willebrand factor and plasminogen activator inhibitor-1 expression.

Metabolism:
Polynucleotides are metabolized via nucleases, nucleotidases, nucleosidases, deaminases, and phosphorylases to oligonucleotides, nucleotides, nucleosides, and then to the free 2'-deoxyribose sugar, purine and pyrimidine bases

Contraindications:
Known hypersensitivity to defibrotide or any component of the formulation; concomitant administration with systemic anticoagulant or fibrinolytic therapy

Availability:
FDA approved March 2016

Storage and handling
Store intact vials at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Solutions diluted for infusion in D5W or NS should be used within 4 hours if stored at room temperature or within 24 hours if refrigerated. Discard partially used vials. Side

Effects
Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

4.2 Drug Accountability

The Investigational Pharmacist will manage drug accountability records.

4.3 Drug Ordering

UCSF will obtain defibrotide directly from pharmaceutical company as study supply.

4.4 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per UCSF institutional standards, adhering to applicable local and federal laws.

5 Treatment Plan

5.1 Dosage and Administration

Table 5.1 Regimen Description

Study Drug	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Defibrotide	None	6.25 mg/kg	IV over 2 hours	Q6h	Day prior to start of conditioning through Day +21 Post-HSCT

Treatment will be administered on an inpatient basis.

5.1.1 Dose Modifications and Dosing Delays Tables for Specific Adverse Events

Adverse Event: Bleeding or Hypersensitivity reaction

Grade of Event	Management
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 Resume at same dose level
Grade 3	Discontinue therapy
Grade 4	Discontinue therapy

*Patients requiring a delay of > 2 weeks should go off protocol therapy

5.2 Monitoring and Toxicity Management

Each patient receiving defibrotide will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by patients.

Each patient will be assessed periodically for the development of any toxicity as outlined in Section 6 Study Procedures and Observations. Toxicity will be assessed according to the NCI CTCAE v4.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

We will monitor for incidence of clinically significant bleeding and hypersensitivity reactions:

Hemorrhage: Defibrotide may increase the risk of bleeding (based on increased activity of fibrinolytic enzymes *in vitro*). **Do not initiate therapy in patients with active bleeding**; monitor closely for signs of bleeding. If hemodynamically significant bleeding develops while on therapy, discontinue defibrotide, evaluate/treat the underlying cause, and provide supportive care until bleeding resolves.

Hypersensitivity reactions: Hypersensitivity reactions (e.g., rash, urticaria, and angioedema) have been reported (rare). One patient with a history of previous defibrotide exposure experienced an anaphylactic reaction. Monitor closely for hypersensitivity reactions, particularly in patients who have received defibrotide previously. Discontinue therapy for severe hypersensitivity reactions and treat accordingly; monitor until symptoms resolve.

Acute toxicity will be managed by immediately stopping infusion of defibrotide and holding further doses. Hypersensitivity reactions will be managed per local protocols and standard of care. Further management will depend upon the judgment of the clinician.

5.2.1 Other toxicities:

The toxicities listed below have been reported in patients receiving defibrotide. None have been directly attributable to defibrotide itself.

Cardiovascular: Hypotension, thrombophlebitis

Central nervous system: Cerebral hemorrhage, intracranial hemorrhage

Endocrine & metabolic: Hot flash, hyperuricemia

Gastrointestinal: Abdominal cramps, abdominal pain, bloody diarrhea, diarrhea, gastrointestinal hemorrhage, hematemesis, nausea, vomiting

Genitourinary: Hematuria

Hematologic & oncologic: Hemorrhage, oral hemorrhage, pulmonary hemorrhage

Hypersensitivity: Hypersensitivity reaction

Immunologic: Graft versus host disease

Infection: Infection, sepsis

Renal: Renal failure

Respiratory: Epistaxis, pneumonia, pulmonary alveolar hemorrhage, pulmonary infiltrates

Miscellaneous: Fever

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Table 6.1, Schedule of Study Procedures and Assessments. Screening assessments must be performed within 28 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ± 2 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in the study database. The system is password protected and meets HIPAA requirements.

Patients undergoing tandem autologous transplants will repeat the schedule of procedures and assessments on admission for second transplant.

6.1.1 Pretreatment Period

6.1.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 28 days prior to admission.

- Physical examination
- Vital signs
- Performance Status
- Patient and donor blood type, if eligible

6.1.2 Treatment Period

6.1.2.1 Study Procedures: Treatment (Day of admission through Day +21 post-HSCT)

These procedures must be completed weekly starting the day before the start of alkylating agents or TBI.

- Defibrotide 6.25mg/kg IV Q6h to start at 9 pm (+/- 3 hours) on the day prior to start of conditioning .
- Evaluation of clinical response or deterioration
- Physical examination
- Vital signs
- Performance Status
- Evaluation of adverse events
- Standard labs including
    - CBC with differential and platelet count, reticulocyte count
    - Blood chemistry assessment, including: alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, magnesium, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate
    - Uric acid, LDH
    - Direct antiglobulin test, peripheral smear for RBC morphology,
    - Urine protein concentration, urine protein / creatinine ratio,
    - Complement activity (CH50)
    - Coagulation panel including PT/PTT, d-dimer

6.1.3 Post-treatment/Follow Up Visits

Patients will be followed *weekly until Day +28 then monthly* for up to 6 months after enrollment or until disease progression; exception for patients receiving tandem transplants will be followed *weekly until Day +28 then monthly* for up to 6 months after admission from second transplant or until disease progression. The following procedures will be performed at the Follow Up Visit(s):

- Evaluation of clinical response or deterioration
- Physical examination
- Vital signs
- Performance Status
- Evaluation of adverse events
- Standard labs including
    - CBC with differential and platelet count, reticulocyte count
    - Blood chemistry assessment, including: alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, magnesium, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate
    - Uric acid, LDH, haptoglobin
    - Direct antiglobulin test, peripheral smear for RBC morphology

- Urine protein concentration, urine protein / creatinine ratio
- Complement activity (CH50)
- Coagulation panel including PT/PTT, d-dimer

6.1.4 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen

Table 6.1: Schedule of Study Procedures and Assessments[4]

	Screen	Days Pre-HSCT			Days Post-HSCT				Weeks Post-HSCT					TMA Dx
(+/- in days)	**Admit (-28)**	**Admit**	**-7 (+/- 2)**	**-1 (+/- 1)**	**7 (+/- 2)**	**14 (+/- 2)**	**21 (+/- 2)**	**28 (+/- 2)**	**8 (+/- 7)**	**12 (+/- 7)**	**16 (+/-7)**	**20 (+/- 7)**	**24 (+/-7)**	**Dx (+/-3)**
Informed consent	X													
AE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X
Defibrotide		X	X	X	X	X	X							+/-
Physical exam *		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs *		X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History *		X	X	X	X	X	X	X	X	X	X	X	X	X
Standard Labs[1] *		X	X	X	X	X	X	X	X	X	X	X	X	X
Study Labs[2]		X[3]		X	X		X							X

1. Labs per standard of care should include CBC, complete chemistry, LDH, uric acid, haptoglobin, direct antiglobulin test, peripheral smear for RBC morphology, urine protein concentration, urine protein / creatinine ratio, CH50, coagulation panel.
2. Study labs to include plasma free Hgb, ST2, Ang-2, PAI-1, and hold specimen.
3. +/- 2 day window
4. Patients undergoing tandem autologous transplants will repeat the schedule of procedures and assessments on admission for second transplant, with the exception of screening.

* Standard of care for patients undergoing HSCT

6.2 Usage of Concurrent/Concomitant Medications

Patients on the trial will receive the UCSF standard of care for high risk TMA

- Vitamin D started prior to admission with goal levels of vitamin D, 25 hydroxy level of 30- 60ng/mL
- Allopurinol on admission and continue until Day 0 if uric acids are normal, or longer if uric acids remain high
- Two weeks prior to admission patients will begin Eicosapentaenoic Acid (EPA, a component of fish oil). (dosing: < 6 months: 110 mg PO qday, 6 months – 17 years: 30 mg/kg/day, max 2000 mg/day) divided up to three times per day) which will continue until day +100. EPA will be held when patient is unable to take PO, during periods when the patient's platelet count is < 20 x 10^9/L, for clinical bleeding, prior to procedures (hold at least 4 days prior to procedure)**,** and/or requiring platelets transfusions. Clinical trial evidence for EPA does not support an increased bleeding risk with fish oil therapy, even when used in combination with other agents that may increase bleeding.
- n-Acetylcysteine (NAC) prophylaxis in addition to those doses given on admission, and Day +1 and Day +2 for VOD prophylaxis will be given as 70 mg/kg (rounded to nearest vial size) every 8 hours IV or PO starting day +3 and continued until Day +42 or discharge, whichever comes sooner.

There are no restrictions in concurrent / concomitant medications except per standard of care recommendations for use of defibrotide. Specifically, tissue plasminogen activator (t-PA) is contraindicated due to bleeding risk; use of low doses for clearance of IV catheters is permitted. Administration of other anticoagulants concurrently with defibrotide is at the discretion of the treating physician.

6.3 Dietary Restrictions

None

6.4 Prohibited Medications

Eculizumab if used as prophylaxis for TMA, Ibuprofen or other NSAIDs, aspirin

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy (or Activity)

Incidence of TMA will be calculated on a rolling basis and at completion of the study. If at any time incidence of TMA exceeds 2 patients, the study will be paused and evaluated for futility.

7.2 Definitions

7.2.1 Definition of TMA

Criteria for diagnosis of TMA for purposes of this study will be as follows:

- Evidence of microangiopathy, with an additional item from Category A or B, OR
    - The presence of schistocytes (>2/HPF) in the peripheral blood, or
    - Histologic evidence of microangiopathy on a tissue specimen, or

- Undetectable haptoglobin with increased reticulocyte count

- No evidence of microangiopathy but:
  - 1 item from Category A (evidence of organ dysfunction), AND
  - 3 items from Category B (increased TMA biomarkers)

Category A (clinical markers / organ dysfunction)	Category B (biomarkers)
• Proteinuria • Hypertension • Renal dysfunction	• De novo anemia • Do novo thrombocytopenia • Elevated LDH • Terminal Complement Activation

*Definitions of these criteria are provided below.

Definitions of criteria are adapted from Jodele et al (2015 Blood Rev) and provided below:

Laboratory or clinical marker	Description
1. Lactate dehydrogenase (LDH)	• Elevated above the upper limit of normal for age
2. Proteinuria	• A random urinalysis protein concentration of ≥30 mg/dL or abnormal Pr/Cr Ratio
3. Hypertension	• <18 years of age: a blood pressure at the 95th percentile value for age, sex and height. • ≥18 years of age: a blood pressure ≥140/90 mm Hg.
4. De novo thrombocytopenia	• Thrombocytopenia with a platelet count <50 × 10^9/L or a ≥50% decrease in the platelet count
5. De novo anemia	• A hemoglobin below the lower limit of normal for age anemia requiring transfusion support
6. Evidence of microangiopathy	• The presence of schistocytes (>2/HPF) in the peripheral blood, or • histologic evidence of microangiopathy on a tissue specimen, or • Undetectable haptoglobin with increased reticulocyte count
7. Terminal complement activation	• Elevated plasma concentration of sC5b-9 above upper normal laboratory limit
8. Renal dysfunction	• Elevated creatinine above upper limit of normal not due to alternative cause (e.g., drug, fluid status)

7.2.2 Definition of Severe TMA

Any TMA meeting criteria described in 7.2.1 with any of the following additional features:
• Renal dysfunction requiring dialysis
• Pleural or pericardial effusion requiring any medical or surgical intervention
• CNS dysfunction including seizure
• Inpatient admission > 90 days duration directly related to TMA management

7.3 Evaluation of Safety and Toxicity

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug. This includes measuring incidence of hemodynamically significant bleeding or bleeding that results in life-threatening or permanent clinical sequelae.

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.03 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events.

7.4 Definitions of Adverse Events

7.4.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.4.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.4.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.4.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that

has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.4.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor (The University of California, San Francisco), it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are 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 one 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.

7.4.2.4 Life-threatening

An adverse event or suspected adverse reaction 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 adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.5 Recording of an Adverse Event

All grade 3 and above adverse events will be entered into the study database, whether or not the event is believed to be associated with use of the study drug. Safety data (SAEs) will be collected from the time of admission until the day after completion of defibrotide (6-12 times the half-life of the study drug). Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into the study database using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0 No AE (or within normal limits)

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

7.6 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.7 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into the study database, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF's Institutional Review Board, the Committee on Human Research (CHR).

All adverse events entered into the study database will be reviewed by the Study Committee on a monthly basis. The Study Committee will review and discuss at each meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

All grade(s) 3-5 adverse events entered into the study database will be reviewed on a monthly basis at the Study Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into the study database, will be reviewed and monitored by the study committee on an ongoing basis and discussed at study meetings, which take place every eight weeks.

7.8 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the study Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 6.1.30)
- Unexpected (as defined in 0)
- Serious (as defined in 6.1.5)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Reporting to Pharmaceutical Companies providing Study Drug

- Reporting to Jazz Pharmaceuticals
    - The SI must send all SAEs (initial and follow-up) that require collection and reporting per protocol, and which occur in a subject who received a Jazz Pharmaceuticals product as study drug, to the Jazz Pharmaceuticals Drug Safety Department within 1 business day of their awareness of the SAE (AEreporting@jazzpharma.com).
    - The SI will report the SAEs using a US-FDA Form 3500A (MedWatch form). [Note: the MedWatch form, is available at http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082728.pdf]
    - The SI must also provide Jazz Pharmaceuticals Drug Safety Department (PVcomms@jazzpharma.com) with a copy of all submissions made to the FDA at the time the submission is made.
    - In addition, all other adverse events will be reported to the Jazz Pharmaceuticals Drug Safety Department in summary or line-item form upon Jazz Pharmaceuticals' request and at the conclusion of the study.

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

- Open label non-randomized un-blinded study to determine feasibility, safety, and efficacy.
- Feasibility endpoints;
    - Incidence of discontinuation of defibrotide. Study will be suspended if defibrotide is not tolerated as outlined below:

N (accrued)	0-6	7-12	13-18	19-24
Evaluate if discontinued in this many or more patients:	5	8	10	12

- Safety endpoints
    - Incidence of reportable SAE's (possibly drug-related and severe or unexpected). Study will be suspended if reportable AE's

N (accrued)	0-6	7-12	13-18	19-24
Evaluate if drug-related SAE's occur in this many or more patients:	4	7	10	12

- Incidence of TMA
    - Historical incidence: 7 of 22 (31.8%). With N=24, study will have 80% power to detect a statistically significant difference if incidence in this treated cohort is 8% or less.
    - Study will be re-evaluated if 2 patients develop TMA as this will render the secondary endpoint futile. May continue enrollment to determine feasibility and safety or expand the patient cohort.
- Incidence of Severe TMA
    - Historical incidence: 6 of 22 (27.3%). With N=24, study will have 70% power to detect a statistically significant difference if incidence in this treated cohort is 4% or less.
    - Study will be re-evaluated if 1 patient develops severe TMA as this will render the secondary endpoint futile. May continue enrollment to determine feasibility and safety or expand the patient cohort.

8.1.1 Study Design

Single arm un-blinded non-randomized Phase II study.

8.1.2 Randomization

No randomization is planned.

8.1.3 Un-blinding Subjects

No blinding is planned.

8.1.4 Stratification Factors

No stratification is required; all patients will receive the same treatment and follow the same assessment procedures.

8.2 Determination of Sample Size and Accrual Rate

Based on historical controls, we estimate accrual of 12 patients per year, with a goal of 24 patients by 2 years.

8.2.1 Sample Size and Power Estimate

Assuming an historical rate of severe TMA of 28%, alpha=5%, and N=24, power to detect a statistically significant value of 4% in this cohort is 92%. The minimum number of patients to enroll to achieve 80% power to detect a difference, assuming a 4% incidence in this cohort, is N=19. Assuming a sample size of N=24, the study has 80% power to detect a statistically significant difference if the incidence of severe TMA in this treated cohort is <5%. Given the small sample size, adjustments for multiple comparisons will not be made.

8.2.2 Replacement Policy

Patients that discontinue participation for reasons other than direct defibrotide toxicity or failure of feasibility will be replaced with additional patients. This included patients who are no longer evaluable for TMA due to mortality prior to week 24.

8.2.3 Accrual estimates

Based on historical rates we estimate accrual of 12 patients per year.

8.3 Interim Analyses and Stopping Rules

Stopping rules as described in section 8.1.

8.4 Analyses Plans

8.4.1 Analysis Population

The analysis population will include all the patients who enroll that receive defibrotide.

8.4.2 Primary Analysis (or Analysis of Primary Endpoints)

The primary efficacy analysis will be performed using the ITT population. The primary endpoint will assess the safety and feasibility of defibrotide. It will compare how many patients received the drug versus how many were intended to receive it. It will look into how many patients stopped the drug early and reasons for this.

8.4.3 Secondary Analysis (or Analysis of Secondary Endpoints)

This will include the incidence of TMA in the patients enrolled on study compared to historical controls, including their demographics, underlying diagnosis, conditioning regimens and other transplant complications. Also will compare incidence of severe TMA compared to historical controls and the complications.

8.4.4 Other analyses/Assessments

Other analysis include incidence of TMA by Day +30 post-HSCT, non-relapse mortality by Day +100 and by Day +180 post-HSCT. Summaries for biomarkers will be provided. Additional exploratory analyses may be performed based on incidence of elevation of single or combination of biomarkers predictive of development of TMA.

8.5 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.03.

8.6 Study Results

Study results will be made available on ClinicalTrials.gov and will be published once the study has completed enrollment and all patients have completed the required follow-up period.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

*J*The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into the study database via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

9.7 Oversight and Monitoring Plan

The CHR will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

9.8 Regulatory Documentation

Prior to implementing this protocol at the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Committee on Human Research (CHR). Prior to implementing this protocol at the participating sites, approval for the UCSF CHR approved protocol must be obtained from the participating site's IRB.

10 Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the CHR mechanism and the process of informed consent. The CHR reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The CHR also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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11 Appendices

Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Prohibited Medications

Drug	**Trade name (if applicable)**
aspirin	
alteplase (systemic)	Activase
eculizumab (prophylactic)	Soliris
ibuprofen	Advil, Motrin
naproxen	Aleve