Title: Vitamin C Infusion for TReatment In Sepsis and Alcoholic Hepatitis

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Vitamin C Infusion for TReatment In Sepsis and Alcoholic Hepatitis

CITRIS-AH

Protocol Number: 0001

Principal Investigators: Arun J. Sanyal and Alpha A. Fowler

Virginia Commonwealth University

IND Sponsor: Federal Food and Drug Administration

IND # 142244

Funded by: National Institute on Alcohol Abuse and Alcoholism (NIAAA)

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21 January 2020

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the NIAAA Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Vitamin C Infusion for TReatment In Sepsis and Alcoholic Hepatitis
Study Description:	It is our long-term goal to identify relevant "druggable" targets for alcoholic hepatitis (AH) and to translate this knowledge in to effective strategies to prevent and treat AH. This proposal will focus on one key area of unmet need in the field i.e. those with alcoholic hepatitis who have active infection and sepsis. We hypothesize that in patients with sepsis and alcoholic hepatitis, a 96-hour infusion of vitamin C (ascorbic acid, AscA, 200mg/kg/24 hours) will improve hepatic function, be well tolerated, and will attenuate biomarkers of inflammation, vascular injury, and encourage fibrinolysis.
Objectives:	To assess the efficacy of a 96-hour intravenous vitamin C infusion protocol (200 mg/kg per 24 hours) in patients with established alcoholic hepatitis (AH) and sepsis. In this course of performing this proof of concept phase II trial we will explore three hypotheses: *Hypothesis 1A:* Vitamin C infusion will significantly attenuate hepatic dysfunction as measured by the model for end stage liver disease (MELD) score in patients with alcoholic hepatitis and sepsis. *Hypothesis 1B:* Vitamin C infusion will be safe and tolerable in patients with alcoholic hepatitis and sepsis. *Hypothesis 1C:* Vitamin C infusion will attenuate biomarkers of inflammation (C-Reactive Protein, procalcitonin), vascular injury (Thrombomodulin, Angiopoietin-2), while inducing the onset of a fibrinolytic state (Tissue Factor Pathway Inhibitor).

Endpoints:

Primary Endpoint: Change in MELD score at 96 hours as compared to baseline when compared to placebo.

Secondary Endpoints:

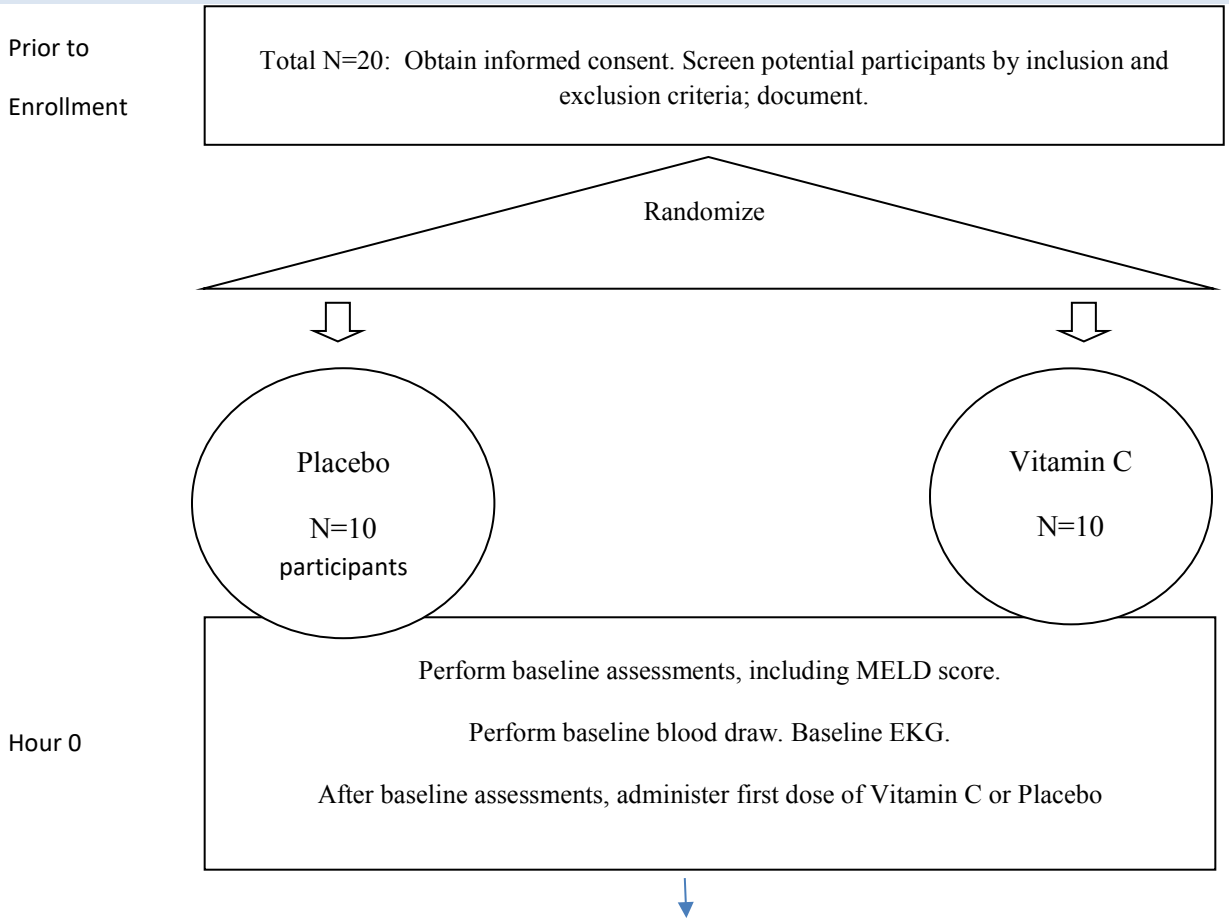
- SOFA Score and components at hours 48, 96, 168
  - PaO2/FiO2
  - SpO2/FiO2
  - Platelets
  - Total Bilirubin
  - Vasopressor status
  - Glasgow Coma Score
  - Creatinine or Urine Output
- CLIF-SOFA scores and components at hours 48, 96, 168
  - Total Bilirubin
  - Creatinine
  - Renal replacement therapy (yes/no)
  - West-Haven grade for hepatic encephalopathy (HE)
  - INR
  - Mean arterial pressure (MAP)
  - Use of vasopressors (yes/no)
  - PaO2 or SpO2
  - FiO2
  - Use of mechanical ventilation (yes/no)
- Lille score
  - Age
  - Albumin (on admission)
  - Bilirubin (on admission, hour 96, 168)
  - Creatinine (on admission)
  - Prothrombin time (on admission)
- Maddrey Discriminate Function (MDF) at hours 96, 168
  - Prothrombin time (hours 96, 168)
  - Total bilirubin (hours 96, 168)
  - PT control/reference level (assuming 12 seconds)
- Liver enzymes and function tests at hours 48, 96, 168
  - AST, ALT, total bilirubin, alkaline phosphatase, albumin
- MELD-Na Score at hours 48, 96, 168
  - INR, creatinine, bilirubin, sodium
- Documented tolerability at hours 24, 48, 96
  - Need for dose reduction, headache, dizziness, dry mouth, nausea, vomiting, flushing, rash, hypotension, treatment related adverse events
- Documented safety at hours 24, 48, 96
  - QTc Interval (EKG)
  - Crystalluria (Urinalysis with microscopy and pH testing)
- Serum Biomarkers
  - Procalcitonin, C-reactive protein, thrombomodulin, thromboelastography (TEG), Receptor for Advanced

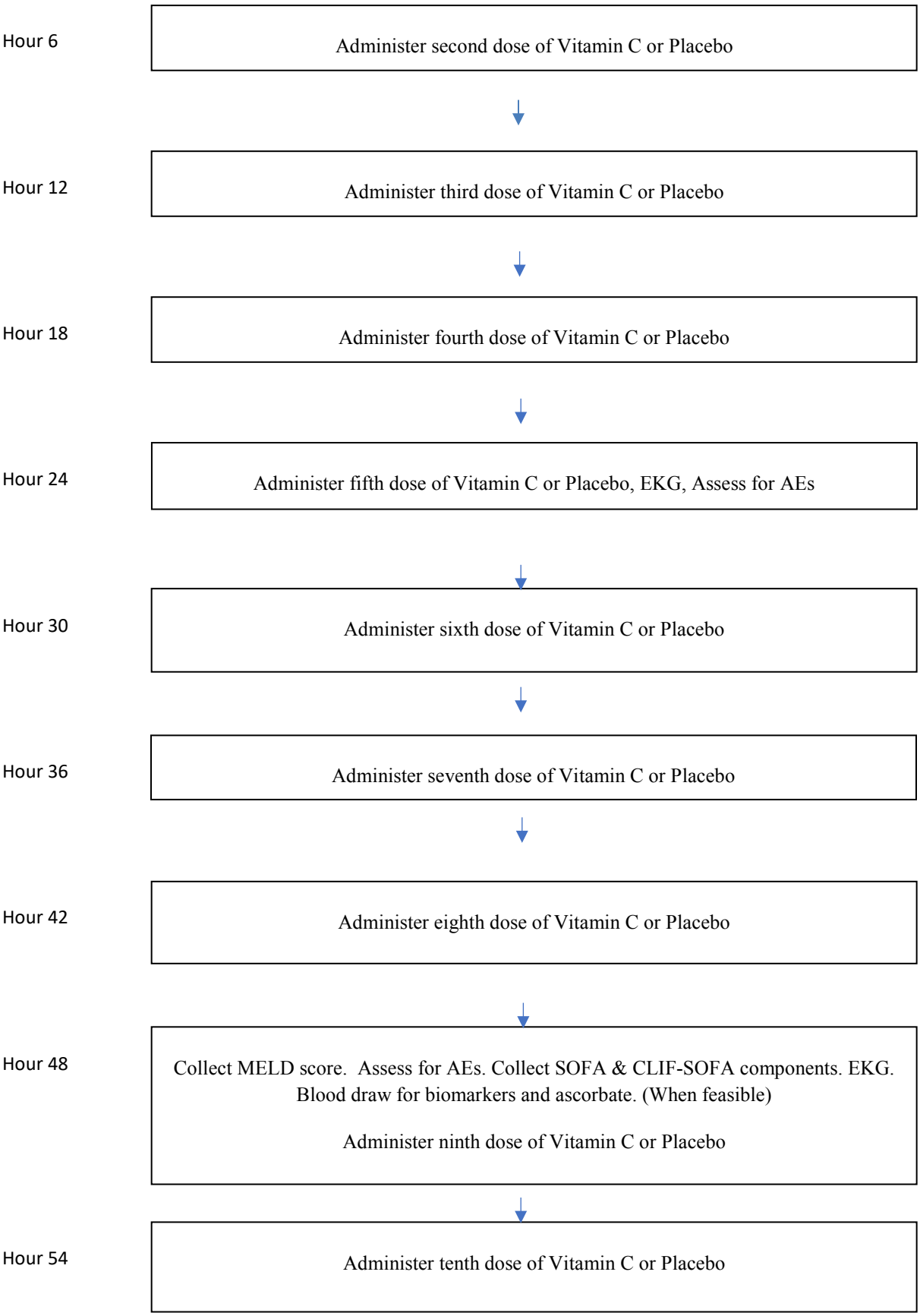
Glycation End Products, Tissue Factor Pathway Inhibitor at study hours 0, 48, 96, 168 (When feasible)

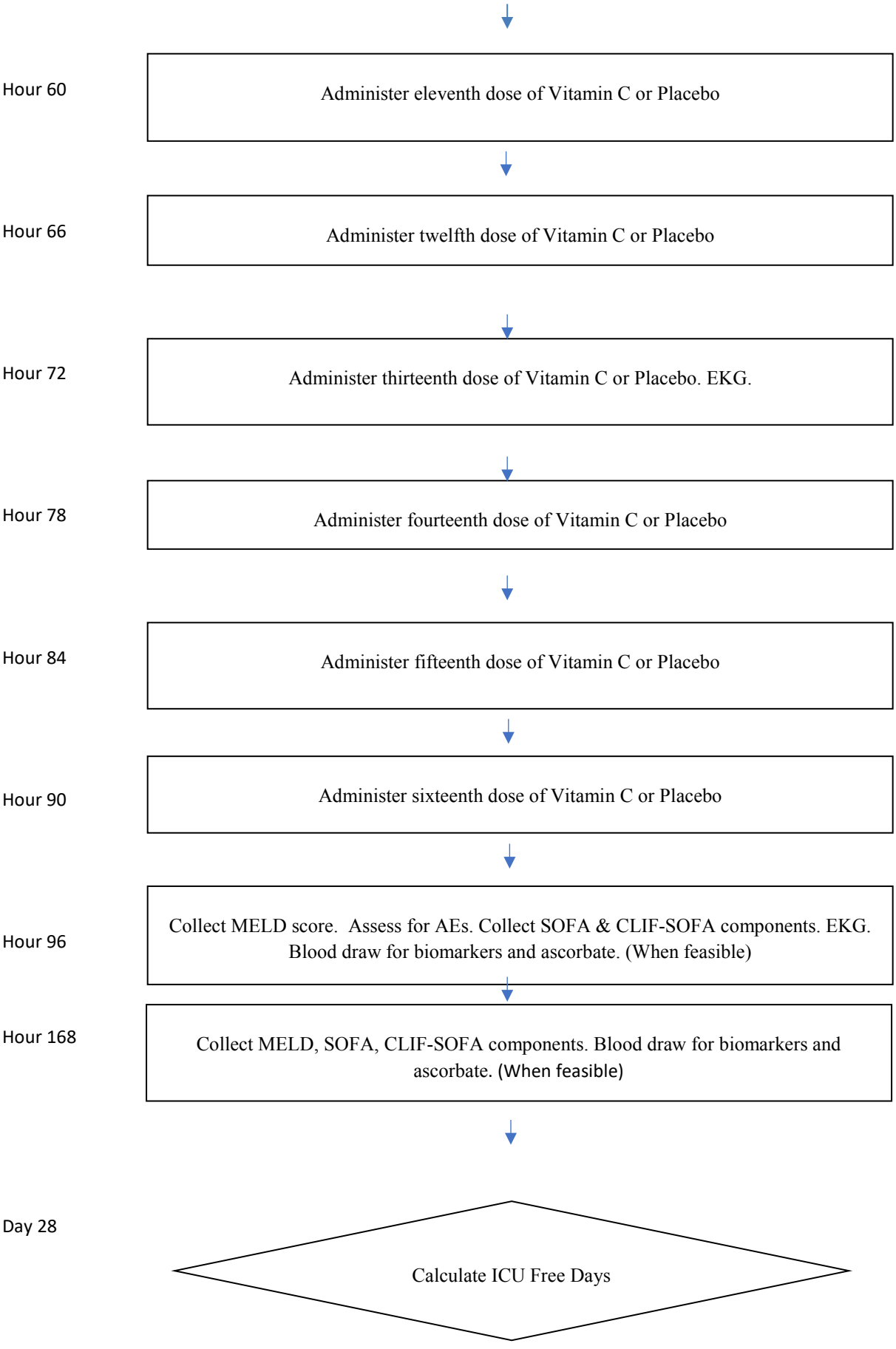
- Ascorbate level at hour 0, 48, 96, 168 (When feasible)
- Need for escalation of support i.e. need for ventilator or pressor support when these are not needed at baseline
- ICU-free days at day 28
- All-cause mortality to day 28 and day 90
- Hospital-free days at day 90

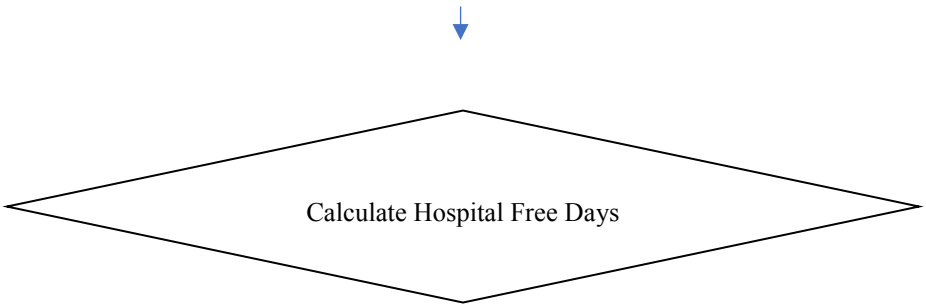
Study Population:	A total of 20 adult subjects with alcoholic hepatitis and suspected or documented sepsis will be enrolled in this study. All participants will be enrolled at the Virginia Commonwealth University Health System (VCUHS).
Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	Subjects will be recruited from the Emergency Department (ED), inpatient medicine unit admitted to the Digestive Health Service (DHS), and Intensive Care Units (ICU) at VCUHS.
Description of Study Intervention:	Participants will be randomized to receive either intravenous Vitamin C (sterile L-ascorbic acid mixed in 5% dextrose in water) or placebo (5% dextrose in water). Active treatment will continue for 96 hours, discharge from study hospital, study withdrawal, or death, whichever comes first.
Study Duration:	Years 1-4
Participant Duration:	90 days

1.2 SCHEMA




Hour 6
Administer second dose of Vitamin C or Placebo
Hour 12
Administer third dose of Vitamin C or Placebo
Hour 18
Administer fourth dose of Vitamin C or Placebo
Hour 24
Administer fifth dose of Vitamin C or Placebo, EKG, Assess for AEs
Hour 30
Administer sixth dose of Vitamin C or Placebo
Hour 36
Administer seventh dose of Vitamin C or Placebo
Hour 42
Administer eighth dose of Vitamin C or Placebo
Hour 48
Collect MELD score. Assess for AEs. Collect SOFA & CLIF-SOFA components. EKG. Blood draw for biomarkers and ascorbate. (When feasible)
Administer ninth dose of Vitamin C or Placebo
Hour 54
Administer tenth dose of Vitamin C or Placebo


Hour 60
Administer eleventh dose of Vitamin C or Placebo
Hour 66
Administer twelfth dose of Vitamin C or Placebo
Hour 72
Administer thirteenth dose of Vitamin C or Placebo. EKG.
Hour 78
Administer fourteenth dose of Vitamin C or Placebo
Hour 84
Administer fifteenth dose of Vitamin C or Placebo
Hour 90
Administer sixteenth dose of Vitamin C or Placebo
Hour 96
Collect MELD score. Assess for AEs. Collect SOFA & CLIF-SOFA components. EKG. Blood draw for biomarkers and ascorbate. (When feasible)
Hour 168
Collect MELD, SOFA, CLIF-SOFA components. Blood draw for biomarkers and ascorbate. (When feasible)
Day 28
Calculate ICU Free Days



Day 90

END STUDY

1.3 SCHEDULE OF ACTIVITIES (SOA)

Assessments	**Hour 0**	**O 24 hrs 1st 7 days or in ICU**	**Hour 48**	**Hour 96**	**Hour 168**	**Day 28**	**Day 90**
VS: BP, HR, MAP, RR, Temp., O2 sats, CVP, Glasgow Coma Scale, West-Haven Scale	**S**		**S**	**S**	**S**		
Body Weight	**S**		**S**	**S**			
Suspected or known site of sepsis	**S**		**S**	**S**	**S**	**R**	**R**
I/Os Total and Urine and urinalysis for crystalluria	**S**	**R**	**R**	**R**			
Assessment of Renal Function with serum creatinine, urine output and Use of Dialysis	**S**		**S**	**S**	**S**	**S**	
Calculate MELD Score (post study by biostatistician)	**S**		**S**	**S**	**S**		
Labs: Arterial Blood Gases, Na+, K+, BUN, Cr, WBC, Hgb, Hct, Platelets, PT/INR	**S**		**S**	**S**	**S**		
Bilirubin Total, AST, ALT, ALP, albumin	**S**		**S**	**S**	**S**		
Need for Vasopressors or Inotropes: Epi, Nor-epi, Phenylephrine, Vasopressin, Dopamine	**S**		**S**	**S**	**S**		
All concomitant medications including: Methylprednisone, Hydrocortisone, N-acetylcysteine, Antibiotics, Thiamine, Albumin	**S**		**S**	**S**	**S**		
AE/SAE Assessments	**R**		**R**	**R**	**R**		
Blood for Biomarkers and TEG	**R**		**R**	**R**	**R**		
ICU Free Days						**R**	
Hospital Free Days							**R**
Glucose Monitoring	**S**	**S**	**S**	**S**	**S**		
EKG Monitoring	**S**	**R**	**R**	**R**			
All-Cause Mortality						**R**	**R**

S = Standard of Care
R = Research

2 INTRODUCTION

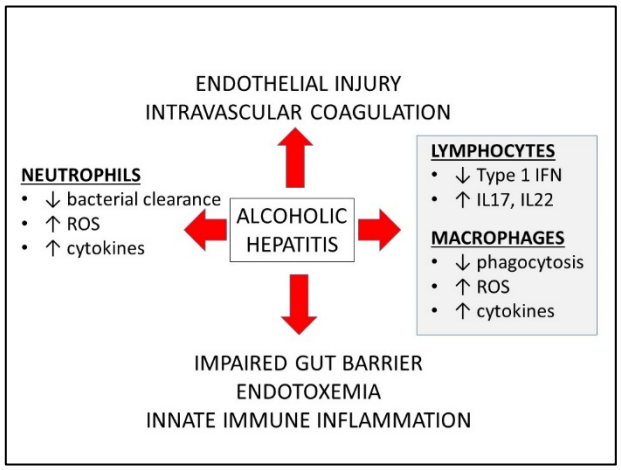
2.1 STUDY RATIONALE

Alcoholic hepatitis is a clinical syndrome characterized by development of rapid onset of jaundice and systemic inflammation in the setting of heavy alcohol (1). Recent guidelines have proposed a standardized definition of AH consisting of the clinical development of hepatitis in the setting of heavy alcohol use, along with a serum bilirubin >3 mg/dL, aspartate aminotransferase (AST) >50 IU/ml and <500 IU/ml, an AST: alanine aminotransferase (ALT) ratio of >1.5, and exclusion of other causes of acute hepatitis such as viral, autoimmune, or metabolic etiologies (2). The diagnosis of AH is associated with high rates of mortality (3). Various scoring systems such as the Maddrey Discriminate Function (MDF) Model for End Stage Liver Disease (MELD), and Lille Model have been developed to predict mortality in alcoholic hepatitis patients (4,5).

Recent data indicated the mortality due to alcoholic cirrhosis is increasing, in particular younger people age 25-34 (6). The main driver of morbidity and mortality in AH patients are infections (7). However, clinical trials of AH exclude patients with suspected or documented infection (8). There are currently no FDA approved therapies for AH. Current guidelines by the American Association for the Study of Liver Disease (AASLD) recommend corticosteroids for the treatment of severe AH (9). However, corticosteroids only have a short-term mortality benefit at 28 days and are associated with higher risks of infection, so therefore contraindicated in patients with AH and suspected or documented sepsis (10).

In this study, we will test the novel hypothesis that high-dose ascorbic acid (AscA or Vitamin C) will improve outcomes of AH patients with sepsis.

2.2 BACKGROUND



AH is associated with numerous pathophysiological mechanisms that increase predisposition to sepsis (Figure 1) (11). High levels of alcohol consumption impair the gut epithelial barrier and increase bacterial translocation and endotoxemia (12). In animal models, alcohol ingestion also increases markers of oxidative stress (13). Activated Kupffer cells and hepatocytes are the likely source of free radicals (14,15). Oxidative stress mediates alcohol induced liver injury via cytochrome P-450 system and leads to mitochondrial damage, activation of apoptosis, and up regulation of lipid synthesis (16, 17,18,19). There is also a release of damage and pathogen associated molecular pattern (DAMP and PAMP) signals that enhance activation of the innate immune system (20) These signals set up a systemic inflammatory state which is further amplified by the systemic response to infection (21) At the same time, there are changes in neutrophil, lymphocyte and macrophage function that impair the ability to clear infection while enhancing oxidative stress and tissue injury (22 23).

Use of High Dose Ascorbic Acid in Patients with AH and Sepsis

Vitamin C or Ascorbic acid (AscA) has been shown to have pleotropic effects in sepsis such as reducing oxidative stress, improving neutrophil function and bacterial clearance, reducing systemic inflammatory cytokines, and improving endogenous catecholamine synthesis (Figure 2) (24, 25, 26, 27). AscA cannot be synthesized in humans and serum levels are dependent on diet (28). Serum levels of AscA are reduced in patients with sepsis and lower levels correlate with higher mortality (29). AscA levels in serum and liver tissue have been shown to be reduced in patients with alcoholic liver disease (30). In critically ill patients, intravenous administration of AscA is necessary to maintain supra-physiological levels (31, 32). In a phase 1 randomized clinical trial of patients with severe sepsis, high dose intravenous AscA was safe with no adverse events and demonstrated a reduction in inflammatory markers and organ dysfunction compared with placebo (33). Previous clinical trials in AH have only administered anti-oxidants via the oral route and excluded patients with infection (34). Therefore, the purpose of this clinical trial is to examine the safety, tolerability, and efficacy of high dose intravenous AscA in patients with severe AH and sepsis.

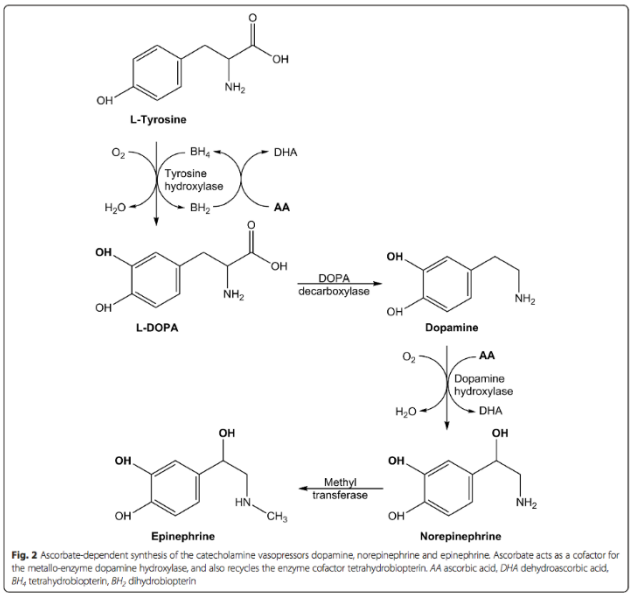


Fig. 2 Ascorbate-dependent synthesis of the catecholamine vasopressors dopamine, norepinephrine and epinephrine. Ascorbate acts as a cofactor for the metallo-enzyme dopamine hydroxylase, and also recycles the enzyme cofactor tetrahydrobiopterin. *AA* ascorbic acid, *DHA* dehydroascorbic acid, BH_4 tetrahydrobiopterin, BH_2 dihydrobiopterin

Preliminary Data To Support the Use of AscA in AH and Sepsis

AscA prevents pulmonary neutrophil infiltration in a feces-induced peritonitis (FIP) model of sepsis (Figure 3).

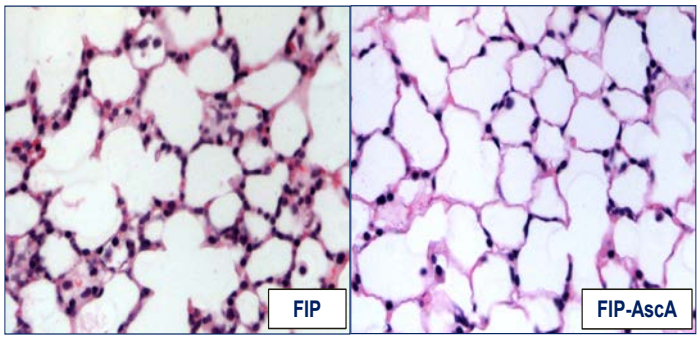
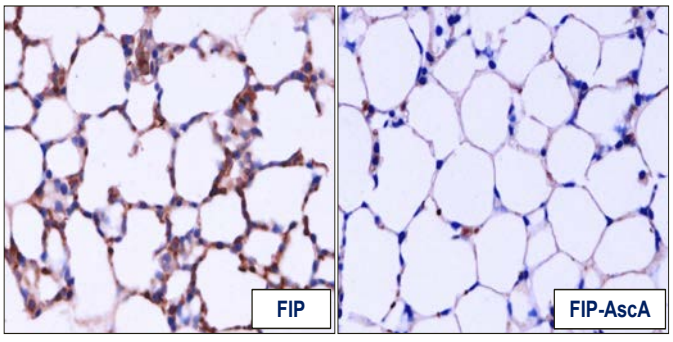


Figure 3a: AscA (200 mg/kg) infused 30 min following onset of feces Induced peritonitis (FIP) attenuates sepsis-mediated acute lung injury in wild type mice at 16 hours. (H&E stain, 40X magnification)



<u>Figure 3b</u>: AscA (200 mg/kg) infused 30 min after feces induced peritonitis significantly attenuated neutrophil sequestration in muring lung at 16 hours. (Anti-murine PMN monoclonal antibody, 40X Mag)

AscA Increased Clearance of Bacteria from Circulation in a Preclinical Model of Sepsis

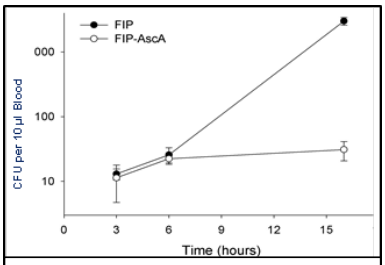


Figure 4: Blood cultures from septic mice after FIP onset. AscA treated mice (200 mg/kg) show significantly lower colony forming units per 10 µl of blood compared to untreated septic animals.

In the same murine model of sepsis, blood was obtained by cardiac puncture at the time of euthanasia using sterile technique varying time points after induction of feces induced peritonitis with or without associated AscA administration (Figure 4). 10 µl of blood was plated on agar plates and colonies counted after overnight incubation. AscA treated mice had a highly significant decrease in colony counts compared to untreated mice ($p < 0.01$). Bronchoalveolar lavage in these mice also demonstrated an increased in alveolar protein content after induction of FIP and protection from AscA (data not shown).

Human Data to Support the Safety and Efficacy of AscA in Humans with Sepsis

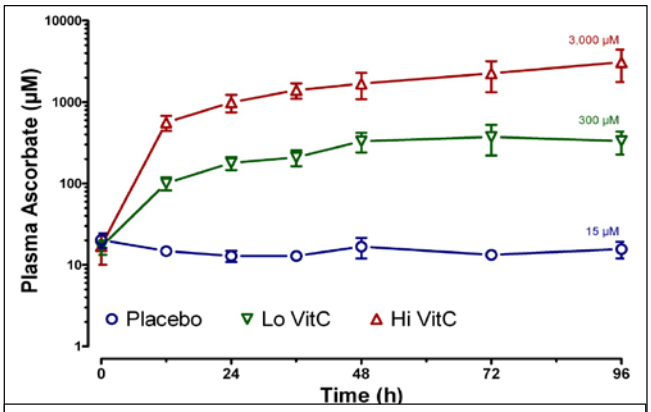


Figure 5: Patients with severe sepsis have low plasma ascorbate levels. Intermittent intravenous vitamin C infusion produces rapid, sustained increases in plasma ascorbate levels.

A phase I, randomized, double blind, placebo-controlled trial, testing the safety of parenteral vitamin C in patients with severe sepsis was initiated at the VCU Medical Center. All patients enrolled, regardless of study arm, received full ICU standard of care. Patients were randomized to placebo (5% dextrose/water, D5W), or low dose vitamin C (50 mg/kg/24hr), or high dose vitamin C (200 mg/kg/24hr). The calculated 24 hour dosage was divided into four and administered intravenously (in 50 ml D5W) over 30 minutes every 6 hours for 96 hours. Vital signs were monitored every 5 minutes during infusion and for 45 minutes afterwards by bedside ICU Nursing and the investigative team. Plasma AscA was measured by HPLC at varying time points after entry (Figure 5). At entry, the levels were sub-normal in all cases.

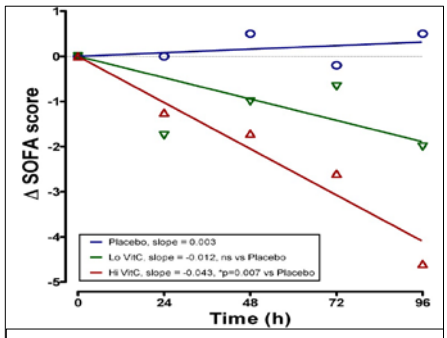


Figure 6: High dose vitamin C significantly reduces sequential organ failure assessment (SOFA) scores during the 96 hour treatment period when compared to placebo.

While they did not change in the placebo arm, both high-dose and low dose AscA achieved steady state within 24 hours. AscA improved SOFA scores (Fig 6). The SOFA scores were plotted over time of entry. While the placebo arm remained relatively flat with a small trend upwards, both low and high dose AscA decreased the SOFA scores over the 96 hours of infusion.

AscA produced a trend towards decreased mortality (Figure 7): In this pilot study which was not powered to evaluate mortality, there was a trend for decreased mortality at day 28. These data formed the basis for an ongoing phase 2B trial of AscA for severe sepsis funded by the NHLBI and led by the Dr. Fowler (co-PI).

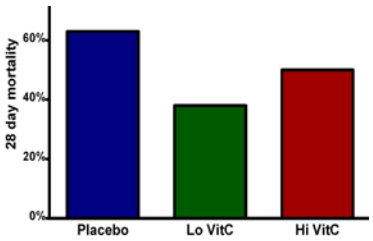


Figure 7: Vitamin C infusion reduces 28-day mortality in patients with severe sepsis

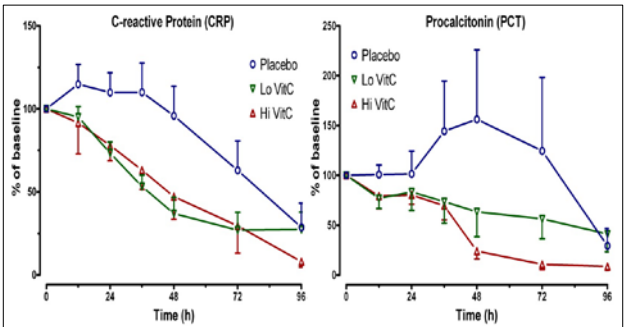


Figure 8: Intravenous vitamin C rapidly lowers inflammatory biomarkers (CRP, PCT) in patients with severe sepsis

AscA decreased hsCRP and procalcitonin: In the placebo arm, the CRP (left panel) and procalcitonin (right panel) remained flat and then either decreased (CRP) or showed an increase (procalcitonin). In contrast, both doses of AscA reduced both hsCRP and procalcitonin (Figure 8).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential Physical Risks of Ascorbic Acid Infusion: dry mouth, nausea, vomiting, dizziness, headache, pseudohyperglycemia (if checked with point of care glucose testing), crystalluria.

Potential Psychological, Social, Legal Risks of Ascorbic Acid Infusion: No psychological, social or legal risks are identifiable from an extensive literature search.

Risks of Blood Draws: All patients will have blood drawn for research purposes. Most blood will be drawn through indwelling catheters. Risks of drawing blood percutaneously are uncommon and include bleeding and bruising.

Glucose Monitoring Plan:

Guidance for blood glucose monitoring in patients enrolled in the CITRIS-AH Trial:

Ascorbic acid is known to artefactually raise POC blood glucose readings by all POC devices except the StatStrip glucometer. However, it does not raise blood glucose readings from a basic metabolic panel or glucose results using the gas lab. Thus, extreme care must be taken to assure an accurate blood glucose level from a metabolic laboratory (BMP) or arterial blood gas panel before initiating any insulin therapy, including sliding scale or scheduled insulin.
Inpatient units not using the StatStrip POC glucometer should follow the guidelines below.

Guidance for blood glucose monitoring in patients enrolled this study:

- Critical care and Inpatient Unit (Main 9 West) Nursing and Physician leadership at all study sites must be informed of vitamin C's effect on point of care (glucometer) blood glucose and arterial blood gas glucose point of care values.
- In-service training will be documented in the Study Training Log
- Bold signage will be displayed on all study instructions, data collection forms, and at the patient's head of bed, stating:
  - ❖ STOP! Do not use Accuchek or other Point of Care devices to measure glucose on this patient
  - ❖ Use only metabolic or gas lab glucose screening methods
  - ❖ This patient is enrolled in a study with Vitamin C, which artefactually increases POC glucose testing
  - ❖ Do Not Initiate or Utilize Sliding Scale, Scheduled Insulin, or Continuous Insulin Infusion Without Laboratory Confirmation of Blood Glucose
- Those receiving insulin infusion or sliding scale insulin as a part of standard of care will have metabolic glucose screening on the schedule determined by the attending physician
- Blood glucose monitoring for insulin administration guidance should only be by a metabolic or blood gas laboratory measured blood glucose results, whether or not the study patient is receiving insulin
- Study personnel will follow each study patient closely to monitor insulin use to ensure that point of care glucose screening is suspended for the research subject.
- Point of care glucose testing may resume 36 hours after the last infusion of study drug.

2.3.2 KNOWN POTENTIAL BENEFITS

Most observational studies suggest a mortality benefit from prior or in-patient Vitamin C use after hospitalization for serious infections. None of the observational trials have reported significant Vitamin C-related toxicity. An animal model of acute lung injury with intravenous LPS and feces induced peritonitis demonstrate significantly less lung injury with Vitamin C, which may result in shortening the time patients require mechanical ventilation.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The identifiable risks arising from exposure to intravenous ascorbic acid infusion are low. In preliminary data analyzed at VCU for another intravenous Vitamin C in sepsis study, we extensively outlined the potential benefits brought by attenuation of acute lung injury and organ failure associated with bacterial sepsis. Given the low risk associated with ascorbic acid infusion and the potential high likelihood of benefit we assess the risk/benefit ratio to be low (i.e., that benefit far outweighs risk).

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Vitamin C infusion will significantly attenuate hepatic dysfunction as measured by the model for end stage liver disease (MELD) score	Change in MELD score at 96 hours as compared to baseline when compared to placebo.	MELD score is an independent positive predictor of mortality in patients with AH.
Secondary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Vitamin C infusion will be safe and tolerable in patients with severe alcoholic hepatitis .	Documented side effects and serious adverse events at hours 24, 48, 96 when compared with hour zero in high dose ascorbic acid versus placebo.	AscA infusion may cause dry mouth, nausea, vomiting, dizziness, headache, flushing, rash, diarrhea. AscA can be excreted from kidney and lead to crystalluria, so will monitor urine pH via urinalysis. Will also monitor EKGs for QTc changes.
Secondary		
Vitamin C infusion will attenuate biomarkers of inflammation (C-Reactive Protein, procalcitonin), vascular injury (Thrombomodulin, Angiopoietin-2), while inducing the onset of a fibrinolytic state (Tissue Factor Pathway Inhibitor)	Modulation of available biomarkers	Changes in these biomarkers may provide mechanistic insight into how vitamin C attenuates inflammation
Secondary		
Vitamin C Infusion will improve clinical endpoints in this patient population .	Change in SOFA Score and Components at hours 48, 96, 168 Change in CLIF-SOFA scores and Components at hour 48, 96, 168 when compared to placebo Change in MELD-Na, MDF, Lille scores at hour 48, 96, 168 when compared to placebo Ascorbate level at hour 0, 48, 96, 168 (When feasible) ICU-free days at day 28 All-cause mortality to day 28, 90 Hospital-free days at day 90	CLIF-SOFA, MDF, MELD, and Lille scores are associated with mortality in alcoholic hepatitis. Ascorbate levels are associated with mortality in sepsis patients in the ICU. AH patients have prolonged hospitalizations and are frequently in the ICU.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Randomization of 20 subjects with AH and sepsis to receive either *Placebo* (50 ml of 5% dextrose in water every 6 hours for 96 hours, or 16 total doses) or *Vitamin C* (sterile L-ascorbic acid for injection at

200 mg/kg per 24 hours with entire calculated 24 hour dose diluted in 200 ml of 5% dextrose in water). One fourth of the 24 hour calculated dosage will be administered in 30 minute intravenous infusions and occur every 6 hours for a total of 16 doses. Standard of care therapy will be followed in both arms.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The purpose of this study is to assess the efficacy of intravenously infused ascorbic acid therapy for patients with alcoholic hepatitis (AH) and sepsis. By restricting the population to those we believe to have both infection and AH, this study targets a disease process and population that has the highest mortality rate and has been studied in animal models. By focusing on sepsis associated with AH, we have selected a group that has a higher disease burden than AH alone and thus likely to have both increased mortality and an increased opportunity for benefit, including a reduction in hepatic dysfunction and ICU length of stay. In choosing the MELD score as the primary outcome, we will be able to discriminate between hepatic function improvement and risk of mortality. By using secondary endpoints such as CLIF-SOFA, documentation of serious adverse events, and biomarkers of inflammation, vascular injury, and coagulation, as the primary outcomes, we will be able to detect changes in clinical outcomes, assess safety and tolerability of ascorbic acid therapy in alcoholic hepatitis, and potential mechanistic insights that are important for demonstrating proof of concept.

4.3 JUSTIFICATION FOR DOSE

Dosing and bio-distribution data in humans show that pharmacological concentrations of vitamin C can only be attained following intravenous administration (32). Dosage selection for this trial was determined both from animal modeling, examining the biological effectiveness in a lung injury model system and from the recently conducted randomized double blind phase I human sepsis safety trial. The 200 mg/kg/24 hour IV dosing protocol was determined from quantification of plasma ascorbate levels and from assessing the impact on SOFA scores. Further, the dosage was selected following observation of the 200 mg/kg/24 hour regimen on biomarker levels.

4.4 END OF STUDY DEFINITION

Active treatment will continue until 96 hours, discharge from study hospital, study withdrawal, or death, whichever comes first. All subjects will be followed to day 90 for collection of outcomes data even though the study intervention will be completed by 96 hours from randomization at the latest.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

The inclusion and exclusion criteria listed for the CITRIS-AH trial are listed below. The definitions of alcoholic hepatitis and severe sepsis for this study are derived and defined as previously published in the reference literature.

Patients must have a diagnosis from the attending physician or hepatologist of definite or probable alcoholic hepatitis based on NIAAA criteria (2) and suspected or proven infection, and meet 2 out of 4 of the criteria for Systemic Inflammatory Response (SIRS) due to infection or be accompanied by at least 1 criterion for sequential organ failure assessment (SOFA):

1. Alcoholic hepatitis:
    a. Definite NIAAA alcoholic hepatitis
        i. Clinical diagnosis and histological confirmation of features of alcoholic hepatitis
            1. Histological diagnosis: liver biopsy with steatohepatitis, lobular inflammation, Mallory-Denk bodies, hepatocyte degeneration or ballooning, “chicken-wire” or portal fibrosis
            2. Clinical diagnosis:
                a. Chronic alcohol use for at least 5 years (may be intermittent abstinent)
                b. >1 standard drink per day in women and >2 in men
                c. AUDIT score >15
                d. Heavy alcohol use for at least 6 months
                    i. “Heavy use” = average >3 drinks per day (40g) for women and average 4 drinks (50-60g) per day for men
                e. Onset of jaundice within the past 8 weeks
                f. Less than 8 weeks of abstinence before onset of jaundice
                g. Serum bilirubin >3 mg/dL
                h. AST >50
                i. AST/ALT ratio >1.5 and levels <400 IU/L
    b. Probable NIAAA alcoholic hepatitis criteria
        i. Clinical diagnosis based on heavy alcohol use >5 years
        ii. Active alcohol use until 4 weeks prior to presentation
        iii. average >3 drinks per day (40g) for women and average 4 drinks (50-60g) per day for men
        iv. Sudden onset or worsening of jaundice (bilirubin >3 mg/dL) within past 60 days
        v. AST/ALT ratio >1.5 and levels <400 IU/L
        vi. Absence of other causes of liver disease
            1. Negative autoimmune markers (ANA < 1:160, SMA <1:80)
            2. Negative viral hepatitis markers (HAV A IgM, HBV sAg, HBV c IgM, HCV Ab, HCV RNA)
            3. No recent exposure to drugs with DILI potential, as determined by attending physician or hepatologist medication review
    c. Patients with potential cofounders may be offered transjugular liver biopsy to assess for histological characteristics of alcoholic hepatitis and ruling out other features of chronic liver disease as a part of standard of care
2. Suspected or proven infection: (e.g., thorax, urinary tract, abdomen, skin, sinuses, central venous catheters, and central nervous system.)
3. The presence of a systemic inflammatory response: Defined as: fever: >38ºC (any route) or hypothermia: <36ºC (core temp only), tachycardia: heart rate > 90 beats/min or receiving medications that slow heart rate or paced rhythm, leukocytosis: >12,000 WBC/µL or leukopenia: <4,000 WBC/µL or >10% band forms. Respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 or invasive mechanical ventilation.
4. The presence of sepsis associated organ dysfunction as assessed by SOFA: (any of the following thought to be due to infection)
    a. Sepsis associated hypotension (systolic blood pressure (SBP) < 90 mm Hg or an SBP decrease > 40 mm Hg unexplained by other causes or use of vasopressors for blood pressure support (epinephrine, norepinephrine, dopamine =/> 5mcg, phenylephrine)
    b. Arterial hypoxemia ($PaO_2/FiO_2 \leq 300$) or supplemental O_2 > 6LPM.

c. Lactate > upper limits of normal laboratory results
d. Urine output < 0.5 ml/kg/hour for > two hours despite adequate fluid resuscitation
e. Platelet count < 100,000 per mcL
f. Coagulopathy (INR > 1.5)
g. Bilirubin > 2 mg/dL
h. Glasgow Coma Scale < 11 or a positive CAM ICU score

5. Negative urine or serum toxicology and acetaminophen drug screen

5.2 EXCLUSION CRITERIA

1. Known allergy to Vitamin C
2. Inability to obtain consent
3. Age < 18 years
4. No indwelling central or peripheral venous or arterial catheter in patients requiring insulin in a manner that requires glucose being checked more than twice daily (e.g. continuous infusion, sliding scale)
5. Presence of diabetic ketoacidosis
6. Patient or surrogate or physician not committed to full support (not excluded if patient would receive all supportive care except for cardiac resuscitation);
7. Pregnancy or breast feeding (as documented by urine or serum pregnancy testing)
8. Moribund patient not expected to survive 24 hours
9. Active or history of kidney stone
10. History of chronic kidney disease, stage IIIb or above
11. History of glucose-6-phosphate dehydrogenase (G6PD) deficiency
12. Active malignancy, except non-melanoma skin cancer
13. Uncontrolled upper or lower gastrointestinal bleeding
14. Possible alcoholic hepatitis or other confounding cause of acute hepatitis such as viral, metabolic, autoimmune
15. History of decompensated cirrhosis as indicated by variceal bleeding within 3 months, tense ascites, or hepatocellular carcinoma (HCC)
16. History of liver or other organ transplantation
17. Initial ALT or AST greater than 5 times the upper limit of normal
18. Positive urine or serum toxicology screen and acetaminophen level
19. Non-English speaking
20. Ward of the state (inmate, other)

5.3 LIFESTYLE CONSIDERATIONS

Not applicable to this study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Subjects will be documented in the Study Screening Log when all Inclusion Criteria are met.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of exclusion criteria such as failure to obtain consent, inability to locate LAR, or delay in diagnosis may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients with sepsis and AH will be recruited from the Emergency Department (ED), the medicine inpatient Digestive Health Service (DHS), and the intensive care units (ICU) at Virginia Commonwealth University Health System (VCUHS). VCUHS is a large tertiary care medical center with a large referral base. Annually over 11,000 patient contacts are made for liver disease and 15% of these are for alcohol related liver disease. Study personnel will review patients within the electronic medical record to identify potential candidates for enrollment. Permission to approach patients and/or their families will be requested from the attending physicians in charge of patient care in the ED, inpatient unit (DHS), or the ICU. All patients meeting the inclusion/exclusion criteria will be approached with a consent and will be entered into a screening log. If the patient is not enrolled, the screening log will include information explaining why enrollment did not occur (exclusion criteria, attending physician denial, patient refusal, etc.). If a patient is enrolled in the ICU and meets ICU discharge criteria based on the decision of the ICU attending physician, the patient will be transferred to the DHS inpatient team on Main 9 West (M9W) unit in order to continue the study drug infusion.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

All study drug doses will be administered via central or peripheral line infusion. Should no central or peripheral line be available at scheduled time of infusion, a call should be placed to pharmacy to determine if study drug may be piggybacked into the line that is infusing a different drug. If administering study drug via piggyback is contraindicated, then study drug infusion may be delayed by a maximum of 6 hours. If clinical drug administration schedule is such that study drug will not have an available administration time beyond this delay, a dedicated new line (peripheral or central) should be inserted. Study drug will be blinded using an identical appearing placebo.

6.1.2 DOSING AND ADMINISTRATION

1) **First study drug dose** (L-ascorbic acid or placebo) will be considered "Dose 1" and will be administered within 6 hours of randomization or the earliest available time post any clinically indicated procedure which requires the patient to be off the unit. All doses will be administered in the medicine M9W inpatient unit or ICU. Patients receiving vitamin C will receive 25% of the total daily calculated dosing (200mg/kg/24 hours) and will be infused over 30 minutes for this first dosing.
2) **Subsequent doses** which represent 25% of the day's total dose will be infused every six hours through 96 hours (+/- 3 hours).
   a) Timing of Dose 2 will be triggered by the physician order for q 6 hour administration and will therefore be listed on the bedside MAR. As such, timing of Dose 2 may be out of the +/- 3 hour window and will not trigger a protocol deviation.
   b) If for any reason any other maintenance dose is not administered within window, the dose will be skipped and the next scheduled dose will be given and documented in the data collection tool.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

VCU Investigational Drug Services (IDS) Pharmacy will coordinate acquisition of sterile L-ascorbic acid for infusion from the manufacturer.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

ASCOR vials contain 25,000 mg/50mL of ascorbic acid and is supplied as pharmacy bulk packaging (PBP). The diluted ASCOR solution should appear colorless to pale yellow. Amber shrouding will be used to cover the IV bag. The product labeling will be blinded as to what the actual product is. For example, the drug name and dose will be indicated as per the following: "Caution: New Drug—Limited by Federal (or United States) law to investigational use. Ascorbic acid ____mg or placebo in 50cc D5W". The placebo is a 50 mL bag of 5% dextrose in water.

6.2.3 PRODUCT STORAGE AND STABILITY

ASCOR is light sensitive so light exposure should be minimized and stored per package insert instructions:

Store under refrigeration (2°C to 8°C); protect from light with amber IV bag cover. Infusion solutions prepared by the IDS Pharmacy in the Main Pharmacy IV admixture suite will expire in 24 hours if refrigerated and light-protected. Infusion solutions prepared by the ICU Pharmacy after-hours will expire in 12 hours, if refrigerated and light-protected.

There is published data establishing the stability of admixtures of ascorbic acid to be at least 24 hours stored at room temperature or refrigerated. Also, Dr. Alpha Fowler has unpublished data that was obtained prior to an earlier IND trial (IND #113856) which demonstrates the stability of samples prepared in the same manner as described below.

In the event that amber tubing is not available in hospital pharmacy stock (due to shortage or supply chain delays), clear infusion tubing may be used. The manufacturer of ASCOR has unpublished stability data showing minimal product oxidation for up to 96 hours when exposed to ambient light.

6.2.4 PREPARATION

IDS or ICU (after hours) Pharmacy will mix "study drug" or placebo once every 24 hours in four 50 ml hooded infusion bags and stored in the M9W unit or ICU in the dark at 4ºC. The prepared IV bags will have the IV tubing attached and primed by *the bedside (M9W or ICU) nursing staff*. At designated infusion time, M9W or ICU Nursing will infuse the contents of the light-shielded agent via infusion pump through light-shielded tubing over 30 minutes. Prior studies performed at VCUHS have shown that L-ascorbic acid prepared for infusion in this way remains stable with no quantifiable oxidation.

Study drug / placebo will be prepared in 50 ml D5W bags, USP, using aseptic technique according to USP 797 requirements. All ASCOR pharmacy bulk package vials utilized will be discarded within 4 hours or sooner as per the ASCOR package insert.

For ascorbic acid, the volume of ascorbic acid to be added to the IV bag will be calculated. This same amount of fluid will be drawn out of the D5W 50 mL bag and discarded. Then, the calculated volume of ascorbic acid will be added to the IV bag. As much air as possible will be removed from the IV bag using an empty syringe with needle attached (in order to prevent oxidation). The IV bag will be covered with a light-protective shroud.

For placebo, a 50cc bag of dextrose 5% in water will have the excess air removed from the IV bag as for the ascorbic acid bags (to maintain the blind). The IV bag will be covered with a light-protective shroud (to maintain the blind).

Microbiologic Controls:

Main Pharmacy IV sterile admixture suite consists of an ISO Class 5 open architecture compounding workbench, with an ISO Class 7 positive pressure buffer zone, and an ISO Class 8 positive pressure anteroom. There is continuous monitoring of temperature, humidity, and air pressure. The environmental controls are recertified every 6 months, including viable active air samples. The pharmacy staff monitors monthly surface samples. Compounding personnel must successfully complete media fill testing and gloved, fingertip sampling as per USP 797 regulations. The ICU Pharmacy (used for after-hours dispensing) has an ISO Class 5 laminar airflow hood (Nuaire Class II Type A2 biological safety cabinet) in a segregated compounding area. This biological safety cabinet is recertified every 6 months. ICU compounding personnel must successfully complete media fill testing and gloved, finger-tip sampling as per USP 797 regulations.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

After informed consent is given, a randomized assignment will be made by the VCU Investigational Pharmacy in random batches of 2, 4, or 8 subjects. Eligibility forms confirming eligibility will be transmitted via the OnCore clinical trials software and verified by the VCU Investigational Pharmacy prior to randomization. Investigational Pharmacy at VCUHS will administer either Vitamin C therapy or placebo. The randomization will be stratified to one of the two study arms.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to the protocol will be assessed and verified using participant drug log, review of electronic medical records and review of the eCRF.

6.5 CONCOMITANT THERAPY

Any concomitant medications as part of standard of care (particularly glucose infusion, insulin, albumin, corticosteroids, N-acetylcysteine, and antibiotics) provided will be recorded.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If subjects do not tolerate the drug due to side effects such as nausea, vomiting, flushing, rash, headache, diarrhea, develops crytalluria on urinalysis, or QTc prolongation >50% baseline, we will reduce the subsequent doses by 50%. If the QTc is greater than 550 msec at any time, the drug will be discontinued.

Loss of indwelling venous/arterial catheter or peripheral intravenous access will also trigger the stopping of Vitamin C infusions but subjects will remain on study. Blood glucose monitoring will continue via the central laboratory for 36 hours after the last infusion via peripheral IV draws or peripheral sticks. Biomarker sampling via peripheral IV and/or peripheral stick is allowable as it occurs only 4 times throughout the study and likely only once (if at all) after the patient has been discharged from the unit and is without a central line.

The study drug will be discontinued if a patient develops a metabolic acidosis unexplained by other etiologies (lactic acidosis secondary to septic shock). Determination of the presence of metabolic acidosis will be made by the clinical care team. Study drug will also be discontinued if primary care team or surrogate decision maker request withdrawal. Data collection will continue on these patients following withdrawal of study drug.

Requests to unblind a patient's study treatment can be made to the study (investigational) pharmacist or clinical care team. Unblinding study treatment should occur only in the case of an emergency when knowledge of the study treatment is essential for subject care to treat a serious adverse event and prevent further harm or death.

If possible, a decision to unblind should be discussed with the Principal Investigator or a sub-Investigator prior to unblinding the study treatment.

If a blind is broken (either intentionally or unintentionally), the circumstances should be documented as to who, what, when, and why and all documentation shall be kept by the study pharmacist.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 4-8 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Screening

Subjects will be evaluated for entry into the study according to stated inclusion and exclusion criteria. Individuals who are identified during screening as not eligible for the study need not complete all screening procedures. The reason for ineligible status will be documented on the Screen Failure Log.

The following information will be obtained or performed to evaluate each subject's qualifications for participation in the study:

- Demographic information including gender, date of birth, race, ethnicity
- Medical and medication history over the past 30 days
- Alcohol consumption history
- Collection of blood for chemistry, hematology, coagulation, microbiology, in female patients, a pregnancy test (urine pregnancy test or blood human chorionic gonadotropin (hCG)
- Urinalysis and urine and/or drug/toxicology screening, including acetaminophen
- Physical examination including height and weight (body mass index will be calculated based on these variables), and vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature), skin exam (jaundice yes/no, spider angiomata yes/no), abdominal exam (ascites yes/no, hepatosplenomegaly yes/no) neurological exam (Glasgow Coma Scale, West-Haven Hepatic Encephalopathy Scale, asterixis yes/no)
- Review inclusion and exclusion criteria
- Signed, written informed consent

Assessments at Baseline (Hour 0):

- Collection of concomitant medications (if applicable); including corticosteroids, albumin, thiamine, antibiotics, and N-acetylcysteine use
- Collection of blood for hematology, coagulation, clinical chemistries
- Vital signs and abbreviated physical exam, including Glasgow Coma Scale and West-Haven Scale
- 12-Lead EKG

- Documentation of negative urine or serum drug screen, negative acetaminophen serum level, and negative urine or serum pregnancy testing for human chorionic gonadotropin (hCG) if female

Treatment Day 1 (Hour 24):
- Collection of concomitant medications (if applicable)
- Collection and monitoring of vital signs: blood pressure, temperature, heart rate, oxygen saturation
- Abbreviated physical exam
- Collection of blood for standard of care (SOC) hematology, coagulation, clinical chemistry, and biomarkers
- Document urine volume, urinalysis
- 12-Lead EKG
- AE review and reporting

Treatment Day 2 (Hour 48):
- Collection of concomitant medications (if applicable)
- Collection and monitoring of vital signs: blood pressure, temperature, heart rate, oxygen saturation
- Abbreviated physical exam
- Collection of blood for hematology, coagulation, clinical chemistry, biomarkers
- Document urine volume, urinalysis
- 12-Lead EKG
- AE review and reporting

Treatment Day 3 (Hour 72):
- Collection of concomitant medications (if applicable)
- Collection and monitoring of vital signs: blood pressure, temperature, heart rate, oxygen saturation
- Abbreviated physical exam
- Collection of blood for standard of care: hematology, coagulation, clinical chemistry
- Document urine volume
- 12-Lead EKG
- AE review and reporting

Treatment Day 4 (Hour 96):
- Collection of concomitant medications (if applicable)
- Collection and monitoring of vital signs: blood pressure, temperature, heart rate, oxygen saturation
- Abbreviated physical exam
- Collection of blood for SOC hematology, coagulation, clinical chemistry, and biomarkers
- Document urine volume, urinalysis
- 12-Lead EKG
- AE review and reporting

Study Day 7 (Hour 168):
- Collection of concomitant medications (if applicable)
- Collection and monitoring of vital signs: blood pressure, temperature, heart rate, oxygen saturation

- Collection of blood for SOC hematology, coagulation, clinical chemistry, and biomarkers

Study Day 28
- Phone call or chart review to document morbidity and mortality

Study Day 90
- Surviving subjects will be asked to come for a close out visit. However, this population is notorious for compliance issues and if they do not come in a phone call and chart review will be done along with assessment via national death register

8.2 SAFETY AND OTHER ASSESSMENTS

Assessment of hepatic safety: We will follow the current guidance from FDA for assessment of liver safety in those with pre-existing hepatic impairment. Evaluation of Drug Induced Severe Hepatitis (eDISH): eDISH plots will be overlaid from placebo and drug treated arms at the end of the study to look for DILI signals. Those cases with bilirubin > 3x ULN and ALT > 8x ULN will be studied individually and adjudicated for DILI. These data will be provided to the DSMB for concordance with DILI assessment and to IRB and regulatory agencies.

For individual cases, the following rules will be followed for drug discontinuation for DILI:

Since the study population will have evidence of severe liver injury coming in to the trial, these modifications are proposed.

If AST or ALT rise by > 50% from baseline, but are less than 8 times the upper limit of normal and this is associated with less than 3 mg/dl rise in bilirubin, a hepatic panel will be repeated within 24 hours. If the AST and ALT continue to rise or bilirubin rises by 3 mg/dl or more, the study drug will be discontinued.

If AST or ALT exceed 8 times the upper limit of normal at any time or bilirubin rises by 3 or more mg/dl from baseline within a 48-hour time frame, the study drug will be discontinued.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a 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 functions, or a 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

The following subsections will include a discussion of how AEs will be classified.

8.3.3.1 SEVERITY OF EVENT

All AEs will be assessed by the study clinician using a protocol defined grading system. Describe the method of grading an AE for severity. For example, many toxicity tables are available for use and are adaptable to various study designs. Selection of a toxicity table or severity scale should be made in consultation with the study Medical Monitor.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The Principal and Sub-Investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Investigators will report all unanticipated problems that involve risk or harm to a research participant AND was not anticipated or foreseen (e.g., not described in the consent form) AND is probably or definitely related to or caused by the research to the IRB in the required reporting time frame. The IRB at VCUHS will be notified within 5 business days of receiving notice of the unanticipated problem.

VCU will report all unanticipated problems, defined as problems that involve risk or harm to a research participant AND was not anticipated or foreseen (e.g., not described in the consent form) AND is probably or definitely related to or caused by the research, to the DSMB within 7 calendar days of the being notified of the event.

Investigators will also determine if the serious adverse event is unexpected for Vitamin C. Unexpected for Vitamin C is defined as any event not listed in the Vitamin C package insert. If the investigator determines that any serious and study-related adverse event is unexpected for Vitamin C, the FDA will be notified within 7 calendar days. Such events may also meet the definition of Unanticipated Problems as described below.

Examples of untoward clinical occurrences, or disease-related events (DREs) that are expected in the course of AH include: 1) transient hypoxemia, 2) agitation, 3) delirium or hepatic encephalopathy, 4) nosocomial infections, 5) skin breakdown, 6) gastrointestinal bleeding, 7) acute kidney injury, and 8) worsening of hepatic function. Such events, which are often the focus of prevention efforts as part of usual ICU care, will not be considered reportable adverse events unless the event is considered by the investigator to be associated with the study drug or procedures, or unexpectedly severe or frequent for an individual patient sepsis and AH. Examples of unexpectedly frequent untoward clinical occurrences would be repeated episodes of unexplained hypoxemia. This would be in contrast to an isolated episode of transient hypoxemia (e.g., Sp02 ~85%), related to positioning or suctioning. This latter event would not be considered unexpected by nature, severity or frequency. These events will be captured in the eCRF.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria from the time of consent to through study hour 168 until resolved, withdrawn from the study, death, or lost to follow up:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 48 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 5 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 5 business days of the IRB's receipt of the report of the problem from the investigator.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Our null hypothesis (H_0) is that intravenous infusion of vitamin C at 200 mg/kg/day will not result in decrease in MELD score from admission to day 4 when compared to placebo.

Our alternative hypothesis (H_1) is that intravenous infusion of vitamin C at 200 mg/kg/day will significantly reduce MELD scores at day 4 compared with MELD on admission in patients with alcoholic hepatitis and sepsis.

9.2 SAMPLE SIZE DETERMINATION

We anticipate an average MELD of 29 on enrollment, with a standard deviation of 5 points, which is based on previous analysis of VCU patient data with alcoholic hepatitis and sepsis. If we assume an alpha of 0.05 and power of 80%, we will need to enroll 8 patients in each arm in order to detect a 25% decrease in MELD on day 4. Therefore, we will overpower and enroll 10 patients in each arm given uncertainties of power calculation. Changes from baseline to day 4 will also be compared across arms by Wilcoxon test. Power calculations were made with NQuery 4.0.

9.3 POPULATIONS FOR ANALYSES

We will perform the following analyses for the study:

- *Intention-to-Treat (ITT) Analysis Dataset:* all randomized participants
- *Modified Intention-to-Treat Analysis Dataset*: participants who took at least one dose of study intervention and/or have some particular amount of follow-up outcome data
- *Safety Analysis Dataset:* subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of study intervention
- *Per-Protocol Analysis Dataset:* participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention and will be the primary analysis for all outcomes

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Continuous variables will be compared across groups using ANOVA or a Kruskal Wallis ANOVA depending on their distribution. Changes from baseline to time of measurement will be compared by analysis of covariance. Categorical variables will be measured by Fisher's Exact test. Correlations will be assessed by Spearman's coefficient.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Change in MELD from baseline to day 4. Changes from baseline to time of measurement will be compared by analysis of covariance.

We will use the following MELD formula:
Original MELD Score = (0.957 * ln(Serum Cr) + 0.378 * ln(Serum Bilirubin) + 1.120 * ln(INR) + 0.643) * 10
(if hemodialysis, value for Creatinine is automatically set to 4.0)

Note: If any score is <1, the MELD assumes the score is equal to 1.

9.4.3 SAFETY ANALYSES

Adverse Events

Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be listed by reported verbatim term and MedDRA-preferred term, start and stop date and time, study day, duration, severity, relationship to study drug, and seriousness. Additionally, data may be grouped for analysis by different levels of the MedDRA hierarchy. The incidence of AEs, the incidence of treatment- related AEs, and the severity of AEs will be tabulated by cohort (Vitamin C or placebo). The number and percentage of patients with SAEs and treatment-related SAEs and patients who withdraw due to an AE will be tabulated by cohort (Vitamin C or placebo).

Clinical Laboratory Testing

Clinical laboratory test parameters will be listed for individual patients. Baseline for clinical laboratory parameters will be defined as the last evaluation before the start of the initial dosing with study drug. Summary statistics, including mean absolute change from baseline, will be calculated for each parameter and summarized.

Vital Signs

Vital signs results (systolic and diastolic blood pressure, pulse rate, and body temperature) will be listed for individual patients. Each vital sign measure will be tabulated by evaluation time point. Baseline for vital signs measurements will be defined as the last evaluation before the beginning of the first study drug infusion (Vitamin C or placebo, which will generally be Baseline, pre-dose). Summary statistics, including mean absolute change from baseline, will be determined and tabulated for each measure.

Physical Exams

Physical examination findings at baseline will be listed. Clinically significant changes will be recorded as AEs. Symptoms of interest previously reported with intravenous Vitamin C based on the package insert will be recorded daily, including dizziness, headache, nausea, vomiting, flushing, rash, or diarrhea.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Many of the patients approached for participation in this research protocol will have limitations of decision-making abilities due to their critical illness. Hence, most patients will not be able to provide informed consent. Accordingly, informed consent will be sought from the potential subject's legally authorized representative.

Regarding proxy consent, the existing federal research regulations ('the Common Rule') state at 45 CFR 46.116 that: "no investigator may involve a human being as a subject in research…unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative"; and defines at 45 CFR 46 102 (c) a legally authorized representative (LAR) as: "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." OHRP defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the surrogate to provide consent for subject participation in the research.

According to a previous President's Bioethics Committee (National Bioethics Advisory Committee), an investigator should accept as an LAR…a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place. Finally, OHRP has opined in their determination letters that a surrogate could serve as a LAR for research decision making if such an individual is authorized under applicable state law to provide consent for the "procedures" involved in the research study.

According to the Belmont Report, respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. One method that serves to protect subjects is restrictions on the participation of subjects in research that presents more than minimal risks. Commentators and Research Ethics Commission have held the view that it is permissible to include incapable subjects in research that involves more than minimal risk as long as there is the potential for beneficial effects and if the research presents a balance of risks and expected direct benefits similar to that available in the clinical setting. Several U.S. task forces have deemed it is permissible to include incapable subjects in research. For example, the American College of Physicians' document allows surrogates to consent to research involving incapable subjects only "if the net additional risks of participation are not substantially greater than the risks of standard treatment." Finally, the National Bioethics Advisory Committee (NBAC) stated "that an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the subject, provided that…the potential subject's LAR gives permission…"

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable subjects in research and the previous assessment of risks and benefits in the previous section, the present trial presents a balance of risks and potential direct benefits that is similar to that available in the clinical setting, with the exception of the additional blood draws.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of Data Coordinating Center>. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by <specify name of Data Coordinating Center> research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the <specify name of Data Coordinating Center>.

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data will be stored in the central repository of the NIAAA Alcoholic Hepatitis Network (AlcHepNet) and the VCU lab of Arun Sanyal. The AlcHepNet clinical trial data base and biospecimen databank will be located at the University of Massachusetts Amherst Medical Center. The data will be de-identified and linked to CITRIS-AH study ID number. Future data will be stored indefinitely. At the time of patient screening, a separate informed consent process will occur for enrollment in the NIAAA AlcHepNet Observational Registry. In addition, the CITRIS-AH informed consent form will contain a section to document patient enrollment in the AlcHepNet Registry.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Principal Investigator
Alpha Fowler, MD	Arun Sanyal, MD
Virginia Commonwealth University	Virginia Commonwealth University
P.O. Box 980050 Richmond, VA 23298	P.O. Box 980341 Richmond, VA 23298
804-828-9071	804-828-4060
alpha.fowler@vcuhealth.org	arun.sanyal@vcuhealth.org

University of Massachusetts Medical School Data Coordinating Center Contacts		
DCC Director	**DCC Project Manager/ Biostatistician**	**DCC Database Developer/ Programmer**
Bruce Barton, PhD	Aimee Kroll-Desrosiers, MS	Peter Lazar
AS5-2071 368 Plantation Street Worcester, MA 01605	AS5-2067 368 Plantation Street Worcester, MA 01605	AS5-2063 368 Plantation Street Worcester, MA 01605
508-856-8191	508-856-3540	508-856-8344
bruce.barton@umassmed.edu	aimee.kroll@umassmed.edu	peter.lazar@umassmed.edu

Sub-Investigator	Sub-Investigator	Sub-Investigator
Velimir Luketic, MD	Mohammad Siddiqui, MD	Richard Sterling, MD
Virginia Commonwealth University	Virginia Commonwealth University	Virginia Commonwealth University
P.O. Box 980341 Richmond, VA 23298	P.O. Box 980341 Richmond, VA 23298	P.O. Box 980341 Richmond, VA 23298
804-828-4060	804-828-4060	804-828-4060
velimir.luketic@vcuhealth.org	Mohammad.siddiqui@vcuhealth.org	Richard.sterling@vcuhealth.org

Sub-Investigator	Sub-Investigator	Trainee/Fellow
Richard Stravitz, MD	Scott Matherly, MD	Brian Davis, MD
Virginia Commonwealth University	Virginia Commonwealth University	Virginia Commonwealth University
P.O. Box 980341 Richmond, VA 23298	P.O. Box 980341 Richmond, VA 23298	P.O. Box 980341 Richmond, VA 23298
804-828-4060	804-828-4060	804-828-4060
Richard.stravitz@vcuhealth.org	Scott.matherly@vcuhealth.org	Brian.davis1@vcuhealth.org

Research Nurse	Research Coordinator
Stephanie Taylor	Rebecca Collen
Virginia Commonwealth University	Virginia Commonwealth University

P.O. Box 980341 Richmond, VA 23298	P.O. Box 980341 Richmond, VA 23298
804-828-4060	804-828-4060
Stephanie.taylor@vcuhealth.org	Rebecca.collen@vcuhealth.org

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including gastroenterology, hepatology, and/or pulmonary critical care. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least every 4 weeks after enrollment of the first subject and until the last enrolled subject completes treatment period to assess safety and efficacy data on each arm of the study. The DSMB will also continue to monitor the study every 4-8 weeks until the last subject completes the 90 day end-of-study time period. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study team.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by an internal monitoring team, who may or may not be part of the study team.
- On site monitoring will occur annually at the time of IRB continuing review, and involve random review of certain data to assess for data accuracy, protocol compliance, and deviations.
- The VCU Compliance office will be provided copies of monitoring reports.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at VCU under the supervision of the site investigators. The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the University of Massachusetts Medical School Data Coordinating Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 6 years after study completion.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

ABG	Arterial Blood Gas
AE	Adverse Event
AH	Alcoholic hepatitis
AKI	Acute Kidney Injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibody
ANA	Anti-nuclear antibody
ANCOVA	Analysis of Covariance
AscA	Ascorbic Acid (Vitamin C)
AST	Aspartate aminotransferase
BMI	Body mass index
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DILI	Drug Induced Liver Injury
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial

NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIRS	Systemic Inflammatory Response Syndrome
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2	8/26/2018	Changed title to CITRIS-AH from CITRIS-AI	Standardized terminology
3	8/27/2018	Added additional secondary endpoint clinical features	Clarified clinical details of secondary endpoints
4	8/28/2018	Added justification of endpoints, clinical data for inclusion criteria	Refinement of primary and secondary endpoints needed
5	8/29/2018	Added additional background data on AscA	Previous drafts lacked detailed background AscA data
6	8/30/2018	Added patient recruitment locations	Clarification needed
7	8/31/2018	Added detailed study assessment and procedures	Fixed missing elements
8	9/15/2018	Clarified screening procedures	Changes per IRB request
9	11/15/2018	Added DILI assessment, changed IND exemption to IND pending, IV tubing to be primed at bedside	Changes per discussion with research team and pharmacy
9.1	11/18/2018	Reformatted to DCC NIH template	Additional details on AE, SAE definition, research team contacts
10.1	12/20/2018	Added additional exclusion criteria, specified drug labeling, toxicology assessments, pregnancy assessment, DSMB meeting times	Changes requested by FDA
11	02/25/2019	added crystalluria monitoring, biomarkers to be collected “when feasible”	Reconciled section 1.3 with 8.1
12	1/21/2020	Include statement about using clear IV tubing if amber tubing is not available	Manufacturer of ASCOR has stability data to support use of clear tubing when needed

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