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ASAHI KASEI PHARMA AMERICA

A RANDOMIZED, DOUBLE–BLIND, PLACEBO–CONTROLLED, PHASE 3 STUDY TO ASSESS THE SAFETY AND EFFICACY OF ART-123 IN SUBJECTS WITH SEVERE SEPSIS AND COAGULOPATHY

PROTOCOL NUMBER: 3-001

VERSION: 4.1

FINAL: 28APRIL2017

IND #: 100334

EudraCT No. 2012-002251-42

Sponsor: Asahi Kasei Pharma America Corporation

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28APRIL2017

SIGNATURE **DATE**

This document contains confidential information regarding above clinical study conducted by Asahi Kasei Pharma America Corporation. Upon acceptance of this document, the Investigator and Institution agrees to maintain the information as confidential and limit the access to any such information to only those persons who are under, the Investigator or Institution direct control and, will be engaged in employing such information for the purpose of conducting the study. At no time shall such information be available and employed for any other purposes without prior written approval of Asahi Kasei Pharma America Corporation. This document is prepared in compliance with US 21 CFR Part 312 and in accordance with the ICH E6 Guidance for Good Clinical Practice.

Synopsis

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Assess the Safety and Efficacy of ART-123 in Subjects with Severe Sepsis and Coagulopathy

Name of Sponsor/Company:

Asahi Kasei Pharma America Corporation

Name of Investigational Product:

ART-123

Name of Active Ingredient: thrombomodulin alpha

Objectives

Primary:

- To evaluate whether ART-123, when administered to subjects with bacterial infection complicated by at least one organ dysfunction and coagulopathy, can reduce mortality.
- To evaluate the safety of ART-123 in this population.

Secondary:

- Assessment of the efficacy of ART-123 in resolution of organ dysfunction in this population.
- Assessment of anti-drug antibody development in subjects with coagulopathy due to bacterial infection treated with ART-123.

Study Center(s):	**Phase of Development:**
Global study, up to 350 study centers	Phase 3

Study Period:

Estimated time of first subject enrollment: 3Q 2012

Estimated time of last subject enrollment: 3Q 2018

Number of Subjects (planned):

Approximately 800 randomized subjects.

Diagnosis and Main Criteria for Inclusion of Study Subjects:

This study targets critically ill subjects with severe sepsis requiring the level of care that is normally associated with treatment in an intensive care unit (ICU) setting. The inclusion criteria for organ dysfunction and coagulopathy must be met within a 24 hour period.

1. Subjects must be receiving treatment in an ICU or in an acute care setting (e.g., Emergency Room, Recovery Room).
2. Subjects with:
   a. Clinical objective evidence of bacterial infection and a known site of infection (Refer to Appendix C, Section 15.3).
   b. Current treatment with intravenous antibiotics.
   c. White Blood Cell (WBC) count greater than (>) 12,000/mm^3 or less than (<) 4,000/mm^3 or Bandemia greater than (>) 10%.
   d. Temperature of < 36ºC or fever > 38ºC. For hypothermia, a core reading is preferred.

   Note 1: If a subject has a Gram stain consistent with bacterial infection, positive culture from blood or an otherwise sterile body fluid, observed peritonitis, positive urinary antigen, clinical presentation of meningococcemia, or otherwise compelling evidence of infection as determined by the CCC, only one of the two inclusion criteria # 2c (WBC) or 2d (temperature) is required.

   Note 2: The presence of concurrent fungal or viral infection is allowed for the study entry, provided that the primary reason for treatment is bacterial infection.

3. Subjects with sepsis-associated organ dysfunction **defined by at least one of the following:**
   a. Cardiovascular Dysfunction defined as requiring both adequate fluid resuscitation and vasopressors* to maintain Mean Arterial Pressure (MAP) greater than or equal to (≥) 65 mmHg (implies fluid resuscitation alone does not raise MAP to ≥ 65 mmHg). Adequate fluid resuscitation is defined as:
      - Intravenous administration of at least 20 mL/kg crystalloid or 10 mL/kg colloid infusion within 6 hours.

OR

- Central Venous Pressure (CVP) of greater than (>) 8 mmHg or Pulmonary Artery Wedge Pressure (PAWP) of greater than (>) 12 mmHg.

** If dopamine is the only vasopressor used, the infusion rate must be greater than (>) 5 µg/kg/min (i.e., must be prescribed to support cardio-pulmonary perfusion). If vasopressin is used, it must be given in conjunction with another vasopressor.*

b. Respiratory Dysfunction is defined as the acute need for mechanical ventilation and **PaO2/FiO2 ratio of <250** (**or < 200** when lung is the site of infection). For the purposes of this protocol, mechanical ventilation is defined as any type of ventilation administered via an endotracheal tube or nasotracheal intubation. A simple administration of supplemental oxygen is NOT considered to be mechanical ventilation for the purposes of this study.

4. Subjects with coagulopathy characterized by an INR >1.40 without other known etiology (e.g., anticoagulant therapy, chronic liver disease)

5. Subjects with coagulopathy characterized by platelet count in the range of greater than (>) 30,000/mm^3 to less than (<) 150,000/mm^3 **OR** a greater than 30% decrease in platelets in 24 hours [23, 24, 25, 26, 27, 28].

Investigational Product, Dosage and Mode of Administration:

ART-123 - thrombomodulin alpha:

ART-123 or Placebo, are administered at the equivalent dose of 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day for six days. ART-123 is given by intravenous bolus or rapid IV infusion, in which case 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day is diluted in 50 mL of Normal Saline (NS) and given over a period of 15 minutes. ART-123 **must not** be administered concurrently with any other medications or in the same IV line that is used for administering other medications. If the same IV line that is used for delivery of other medications must be used for administering study drug or placebo then the line **must be flushed with at least 5 mL of 0.9% Saline solution both prior to and following the administration of study drug or placebo**.

ART-123 is supplied as individual glass ampules containing 6.0 mg of formulated drug in 1 mL of total volume, with an overfill of 0.1 mL[*]. Ampules must be refrigerated at 2ºC-8ºC and protected from light during storage.

**Refer to Section 3.1 for complete information about ART-123 drug product.*

Duration of Treatment:

Six (6) days.

Reference Therapy, Dosage and Mode of Administration:

Placebo:

Placebo for this study is supplied as identically labeled, individual glass ampules in 1 mL of total volume, with an overfill of 0.1 mL. Placebo will also be required to be maintained refrigerated at 2°C-8°C and protected from light during storage. Placebo must be administered according to the same procedures and guidelines as ART-123 (i.e., must not be administered concurrently with any other medications and if the same IV line that is used for delivery of other medications must be used, the IV line that is used for administering study drug or placebo must be flushed with at least 5 mL of 0.9% NS solution both prior to and following administration of study drug or placebo).

Criteria for Evaluation:

Efficacy

Primary Efficacy Endpoint:

- 28 day all-cause mortality

Secondary Efficacy Endpoints:

- Follow-up of all-cause mortality at 3 months
- Resolution of Organ Dysfunction through Day 28 as measured by
    - Shock free and alive days
    - Ventilator free and alive days
    - Dialysis free and alive days

Tertiary Efficacy Endpoints:

- Follow-up of all-cause mortality at 6 and 12 months
- Organ Dysfunction (Hepatic, Renal, Respiratory and Cardiac (Septic Shock) at Baseline, Day 3, Day 7, Day 14 and Day 28
- ICU free and alive days through Day 28
- Hospitalization free and alive days through Day 28
- INR at Baseline, Day 3, Day 7, Day 14 and Day 28

Safety

Primary Safety Endpoints:

- Serious Adverse Events
- Major Bleeding Events
- Adverse Events

Secondary Safety Endpoint:

- Anti-drug antibodies

Statistical Methods:

The total sample size is 800 randomized subjects. This sample size is allocated to treatment arms in a 1 to 1 ratio. The Primary Objective will be tested using a stratified Cochran-Mantel-Haenszel test. For sample size and power calculations an un-stratified Cochran-Mantel-Haenszel test has been used. This sample size provides 80% power if the following assumptions are made:

1) 5% two-sided Alpha level

2) 8% treatment effect (24% placebo mortality rate vs. 16% ART-123 mortality rate).

The assumed treatment effect of 8% is based upon the results of post-hoc analyses from the Phase IIb study.

Informed Consent:

Fully informed consent will be obtained before any study specific procedures are performed in accordance with all applicable ethical and regulatory requirements. It is anticipated, by the very nature of the study that many subjects who will be eligible for this protocol will not be able to give fully informed consent themselves due to various reasons including sedation, unconscious state, etc. and at no time will medical treatment be delayed to secure authorized informed consent for study participation. Therefore, the following will be applied as long as your local laws allow:

- Consent from an Authorized or Legally Authorized Representative (AR / LAR) / next of kin / legally appointed individual in person;
- Verbal consent from an AR/LAR / next of kin / legally appointed individual via telephone, confirmed by signed consent form sent by fax or email (at least 2 people from the study site are required, one to administer the informed consent and the second as a witness);

- Consent from a judge or specifically appointed lawyer for this purpose – if required by local regulations;
- In extreme and urgent circumstances when emergent action is required to mitigate the risk of death, it is understood that the presumed will of the subject will be determined by a physician and documented based on his/her knowledge of the study subject. As appropriate, an independent physician, who is a qualified medical doctor with at least one year's experience in intensive care medicine but must be from another department and/or hospital than the investigator, may sign the informed consent for the subject if the local laws, regulations and ethics committees approve this process. In countries where permissible, this independent physician may be from the same department. The study subject must be presented with the informed consent as soon as it is possible and reasonable, and informed consent obtained for continued study participation. The AR/LAR may act as an agent on the subject's behalf once they are available to provide informed consent.

In addition, where local regulatory and/or ethics committees allow, advance consent may be obtained prior to study entry in an attempt to obtain personal consent from the subject themselves. Should a subject who is enrolled in the study on the basis of advance consent subsequently become unable to make medical decisions for him/herself, then the subject's legally acceptable AR/LAR independent physician should be informed of the subject's participation in the trial.

SIGNATURE PAGE

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

PROTOCOL NUMBER: 3-001

IND #: 100334

EudraCT No. 2012-002251-42

PRODUCT NAME: ART-123

STUDY TITLE:

A RANDOMIZED, DOUBLE–BLIND, PLACEBO–CONTROLLED, PHASE 3 STUDY TO ASSESS THE SAFETY AND EFFICACY OF ART-123 IN SUBJECTS WITH SEVERE SEPSIS AND COAGULOPATHY

VERSION: 4.1

FINAL: 28APRIL2017

PROTOCOL APPROVAL

The signature of the Principal Investigator constitutes an agreement that this study will be conducted according to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality. It is agreed that the conduct and results of this study will be kept confidential and that the case report forms and other pertinent data will become the property of Asahi Kasei Pharma America Corporation.

It is agreed that the protocol contains all necessary information required to conduct the study as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board or Ethics Review Committee.

It is agreed that all participants in this study will provide written informed consent in accordance with ICH Guidelines for Good Clinical Practice and the requirements specified in the Code of Federal Regulations (21 CFR Parts 50, 56, 312). All participants will also be informed that their medical records will be kept confidential except for review by authorized representatives of Asahi Kasei Pharma America Corporation and its associates, the U.S. Food and Drug Administration or other regulatory agencies.

PRINT **PRINCIPAL INVESTIGATOR**	**SIGNATURE**	**DATE**

By signing the above I agree to perform the study in accordance with the protocol, ICH Good Clinical Practice (GCP) guidelines, and all applicable regulations.

Table of Contents

LIST OF ABBREVIATIONS	
ABBREVIATION/TERM	**DEFINITION**
ABG	Arterial Blood Gas
ADA	Anti-drug Antibody
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotransferase
AML	Acute Myelogenous Leukemia
ANOVA	Analysis of Variance
APACHE II	Acute Physiology and Chronic Health Evaluation II
APC	Activated Protein C
AR	Authorized Representative
ARDSNet	Acute Respiratory Distress Syndrome Clinical Network
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AVM	Arteriovenous Malformation
bid	Twice daily
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel Test
CRO	Contract Research Organization
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid

LIST OF ABBREVIATIONS	
ABBREVIATION/TERM	**DEFINITION**
CVP	Central Venous Pressure
DIC	Disseminated Intravascular Coagulation
dL	Deciliter
DVT	Deep Vein Thrombosis
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ESRD	End-Stage Renal Disease
eCRF	Electronic Case Report Form
EP2	Early Phase II
EPCR	Endothelial Protein C Receptor
ER	Emergency Room
F1.2	Prothrombin Fragment 1+2
FAP	Full Analysis Population
FDA	Food and Drug Administration
FiO2	Fraction of Inspired Oxygen
GCP	Good Clinical Practices
GI	Gastrointestinal
H	Hour
hCG	Human Chorionic Gonadotropin
h	Hour
HEENT	Head, Eyes, Ears, Nose, and Throat
HMGB1	High Mobility Group Box 1
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit

LIST OF ABBREVIATIONS	
ABBREVIATION/TERM	**DEFINITION**
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product (also known as study drug)
INR	International Normalized Ratio
ISTH	International Society on Thrombosis and Haemostasis
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous
LAR	Legally Authorized Representative
LMWH	Low Molecular Weight Heparin
LP2	Late Phase 2
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MIC	Minimum Inhibitory Concentration
mL	Milliliters
mm^3	Cubic Millimeters
NS	0.9% Normal Saline
OD	Organ Dysfunction
PAI-1	Plasminogen Activator Inhibitor Type-1
PaO2	Partial Pressure of Oxygen in Arterial Blood
PAWP	Pulmonary Artery Wedge Pressure
PI	Principal Investigator
PICD	Patient Informed Consent Document
PK	Pharmacokinetic
PMD	Primary Medical Doctor

LIST OF ABBREVIATIONS	
ABBREVIATION/TERM	**DEFINITION**
p.o.	By Mouth
PP	Per Protocol
PT	Prothrombin Time
PSV	Pressure Support Ventilation
Q	Every
qd	Once a Day
RBC	Red Blood Cells
RR	Recovery Room
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SIRS	Systemic Inflammatory Response Syndrome
SOC	Standard of Care
SOFA	Sepsis related Organ Failure Assessment
SOP	Standard Operating Procedure
SQ	Subcutaneous
TNF	Tumor Necrosis Factor
US	United States
VAV	Volume Assist Ventilation
VC	Volume Control Ventilation
µg/kg/min	Micrograms per kilogram per minute
WBC	White Blood Cell

1 INTRODUCTION

1.1 Overview

Despite significant advances over the past several decades, mortality from sepsis remains unacceptably high. The risk of death is related to the severity of the sepsis, which is characterized in terms of the presence of organ dysfunctions and coagulopathy.

1.1.1 Sepsis

Sepsis has been defined as infection complicated by a systemic inflammatory response syndrome (SIRS).[1,3] A reassessment of sepsis raised concerns that the SIRS criteria were too sensitive, and that the approach to sepsis continued to need refinement.[2,3] Surviving Sepsis Campaign Guidelines provide diagnostic criteria for sepsis as well as a definition of severe sepsis in which the diagnostic criteria for sepsis includes the necessity for infection and inflammatory response, and that severe sepsis is characterized by evidence of organ dysfunction[3].

Numerous therapies intended to target the various biological pathways of sepsis have been tested in large randomized studies, and all but one, Drotrecogin alfa (recombinant human activated protein C, Xigris®), have failed to show evidence of efficacy.[4,5,6] Xigris, which showed evidence of efficacy in early clinical trials, was withdrawn from the market by the manufacturer (Eli Lilly and Co.) on October 25, 2011.

In contrast, mortality has been reduced by improving the technique of mechanical ventilation[7] or the introduction of bundles of treatments that target various physiologic manifestations of sepsis.[8]

1.1.2 Coagulopathy

It has been known for a long time that coagulopathy is associated with increased mortality in sepsis.[9] While thrombocytopenia is an independent risk factor, its role in increased mortality is less clear, and may not be a result of coagulopathy.[10] Disseminated Intravascular Coagulation (DIC) has been well-described as an important risk factor for mortality in sepsis.[11]

Coagulation and inflammatory pathways are intricately linked[12] and thrombomodulin appears to play a key role both as a scavenger and modulator of thrombin activity, and in its role as an endothelial cell surface protein.[13,14]

Some data suggest that anticoagulation may improve survival in sepsis,[15] while some clinical trials of sepsis therapies may have been confounded by concurrent anticoagulation.[16]

Irrespective of these findings, modulation of coagulation is a credible approach towards the realization of improved prognosis for subjects with sepsis and coagulopathy.

1.2 Mechanism of Action

ART-123 is a recombinant human soluble thrombomodulin (thrombomodulin alpha). Endothelial membrane bound and soluble forms of thrombomodulin are part of a network of endogenous anti-coagulant proteins that also possess potent anti-inflammatory activities in the presence of sepsis.[17] The primary mechanism of protection afforded by human recombinant soluble thrombomodulin is derived from its capacity to bind circulating thrombin molecules and serve as an activation complex to convert protein C to activated protein C (APC).

Soluble thrombomodulin possesses an array of activities which are also relevant in its mechanism of protection in sepsis. Soluble thrombomodulin avidly binds thrombin and the thrombin: thrombomodulin complex can no longer bind to fibrinogen substrates to generate fibrin clots. Additionally, thrombin-soluble thrombomodulin complexes activate a plasma procarboxypeptidase B species known as TAFI (thrombin activatable fibrinolysis inhibitor).

Furthermore, soluble thrombomodulin has intrinsic anti-inflammatory properties separate from its ability to inactivate thrombin and generate APC. In experimental models of sepsis soluble thrombomodulin reduces the expression of pro-inflammatory cytokines and chemokines, attenuates endothelial cell adhesion molecule expression, limits neutrophil-endothelial interactions and lowers circulating levels of the late acting mediator of sepsis High Mobility Group Box (HMGB) – 1.[18]

1.3 Previous Clinical Experience for ART-123

Endothelial expression of thrombomodulin is down regulated in sepsis.[19] Phase III studies conducted in Japan, in subjects with DIC due to either infection or hematologic malignancy, showed that ART-123 statistically significantly outperformed heparin in the resolution of DIC, and it appeared to reduce mortality in a prospective subset of subjects with infection.

In a global Phase IIb trial in subjects with sepsis and suspected DIC ART-123 treated subjects had a positive trend of reduced mortality as compared to placebo subjects. Post-hoc analysis of these data indicated that reduced mortality from ART-123 is best predicted when three

factors are present: infection, at least one organ dysfunction, and coagulopathy indicated by prolongation of the INR.

Patients requiring Renal Replacement Therapy (RRT) for chronic or acute renal failure, were prohibited from being included in the previous Phase IIb trial and the current Phase III trial because the clearance of ART-123 in humans is mainly renal and because of the lack of clinical information such as the pharmacokinetics (PK) and safety in this population. In addition, subjects who required RRT post study enrollment were required by protocol to discontinue the study drug administration. A Phase I trial studying the safety and PK of ART-123 subjects with impaired renal function and in healthy subjects with normal renal function was completed. This study included the collection of PK and safety data of ART-123 in end-stage renal disease (ESRD) subjects undergoing hemodialysis. Based on the data from this study the Sponsor has modified the exclusion criteria related to RRT thereby allowing the enrollment of such subjects without any dose adjustment to the study drug.

Over 120,000 subjects have been treated with ART-123 worldwide. Results from pre- and post-marketing studies indicate that ART-123 is safe and well tolerated. Details on all previous investigations using ART-123 can be found in the current version of the Investigator's Brochure.

2 INVESTIGATIONAL PLAN

2.1 Overall Study Design

This is a randomized, double-blind, placebo-controlled, multi-center, parallel-group study of ART-123 in subjects with coagulopathy due to severe sepsis and a concurrent diagnosis of shock and/or respiratory dysfunction that requires mechanical ventilation for hypoxemia. At randomization, subjects who meet all inclusion criteria and no exclusion criteria will be randomly assigned, in a 1:1 ratio, to receive ART-123 in a dose of 0.06 mg/kg/day up to a maximum dose of 6 mg/day or a matching placebo for 6 consecutive days. These doses will be administered as an intravenous bolus injection or diluted in 50 mL of NS and infused over the period of 15 minutes. Blood samples for assessing coagulation and inflammation parameters, ART-123 concentration, organ dysfunction and safety laboratory tests will be obtained between baseline assessments and the end of the study procedures. Safety-related assessments will include reports of adverse events, monitoring for the degree of burden and risk threshold, and assessing continuation of treatment with ART-123/placebo during the dosing period Day 1-6, ECGs and clinical laboratory test results.

2.2 Study Objectives

The primary objectives of this study are:

- To evaluate whether ART-123, when administered to subjects with bacterial infection complicated by at least one organ dysfunction and coagulopathy, can reduce mortality.
- To evaluate the safety of ART-123 in this patient population.

Secondary objectives include:

- Assessment of the efficacy of ART-123 in resolution of organ dysfunction in this population.
- Assessment of antidrug antibody development in subjects with coagulopathy due to bacterial infection treated with ART-123.

2.3 Rationale for Study Design

ART-123 treated subjects with infection and coagulopathy have shown reduced mortality in a Phase III clinical trial conducted in Japan and a positive trend of reduced mortality in a Phase IIb clinical trial conducted globally. These earlier studies used various criteria for DIC to identify subjects with coagulopathy. This DIC based approach was not fully successful in selecting subjects most likely to respond to ART-123, perhaps because of changes in the methods of identifying subjects with DIC. These studies did not require organ dysfunction other than DIC. Analysis of data from the global Phase IIb trial showed that subjects with cardiac or respiratory organ dysfunctions and coagulopathy at study entry had better response to treatment than subjects without these conditions and it was not always feasible to identify the cause of renal or hepatic dysfunction as sepsis or "other".

The population for the present study will be limited to subjects with cardiovascular and/or respiratory dysfunction, plus coagulopathy in addition to infection characterized by a known site of the infection, fever/hypothermia and the typical WBC response to infection (leukocytosis, leukopenia, or left shifted differential count).

For clarity, both cardiovascular and respiratory dysfunction have been defined using well-established criteria, including vasopressor requirement after fluid resuscitation for cardiovascular dysfunction, and mechanical ventilation requiring intubation for hypoxemia ($PaO_2/FIO_2<250$ or $PaO_2/FIO_2<200$ for subjects with a lung infection) for respiratory dysfunction.

Women of child-bearing potential will be allowed into the study if they have a negative pregnancy test (serum or urine hCG) obtained during the current admission to the hospital. The active drug ART-123 has a half-life of approximately 20 hours. Study drug is administered for up to 6 days to subjects who are either in shock and/or on a ventilator. Ten half-lives will have passed 8 days after the last dose; therefore, there is no reasonable likelihood that such study subjects will become pregnant during the period that drug is present in the patient.

The dose and duration of treatment have been established in preclinical and clinical trials.

ART-123 is not expected to affect the underlying condition, i.e., infection, so use of best treatment is ethically mandated and randomization should balance any impact of specific treatments.

Twenty-eight (28) day mortality is the most commonly used measure by scientific and regulatory authorities to assess efficacy of treatment of sepsis, and that will be the primary end point of the study. Secondary end points will evaluate response to treatment in shock, respiratory failure and the use of dialysis.

2.4 Appropriateness of Outcome Measures

Twenty-eight (28) day all-cause mortality is the generally accepted primary efficacy outcome for sepsis treatments. Because ART-123 acts on the coagulation pathway, major bleeding events will be considered as a safety endpoint, together with adverse events and other serious adverse events.

2.5 Study Population

Approximately 800 subjects will be randomized globally.

2.6 Subject Eligibility Criteria

2.6.1 Inclusion Criteria

This study targets critically ill subjects with severe sepsis requiring the level of care that is normally associated with treatment in an ICU setting. The inclusion criteria for organ dysfunction and coagulopathy must be met within a 24 hour period.

1) Subjects must be receiving treatment in an ICU, or in an acute care setting (e.g., ER, RR)

2) Subjects with:

   a. Clinical objective evidence of bacterial infection and a known site of infection (Refer to Appendix C, Section 15.3).

   b. Current treatment with intravenous antibiotics.

   c. White Blood Cell (WBC) count greater than (>) 12,000/mm^3 or less than (<) 4,000/mm^3 or Bandemia greater than (>) 10%.

   d. Temperature of <36ºC or fever >38ºC. For hypothermia, a core reading is preferred.

   Note 1: If a subject has a Gram stain consistent with bacterial infection, positive culture from blood or an otherwise sterile body fluid, observed peritonitis, positive urinary antigen, clinical presentation of meningococcemia, or otherwise compelling evidence of infection as determined by the CCC, only one of the two inclusion criteria # 2c (WBC) or 2d (temperature) is required.

   Note 2: The presence of concurrent fungal or viral infection is allowed for the study entry, provided that the primary reason for treatment is bacterial infection.

3) Subjects with sepsis associated organ dysfunction **defined by at least one of the following:**

   a) Cardiovascular Dysfunction defined as requiring both adequate fluid resuscitation and vasopressors* to maintain Mean Arterial Pressure (MAP) greater than or equal to (≥) 65 mmHg (implies fluid resuscitation alone does not raise MAP to ≥ 65 mmHg). Adequate fluid resuscitation is defined as:

      - Intravenous administration of at least 20 mL/kg crystalloid or 10 mL/kg colloid infusion within 6 hours.

      OR

      - Central Venous Pressure (CVP) greater than (>) 8 mmHg or Pulmonary Artery Wedge Pressure (PAWP) greater than (>) 12 mmHg.

      * *If dopamine is the only vasopressor used, the infusion rate must be greater than (>) 5 µg/kg/min (i.e., must be prescribed to support cardio-pulmonary perfusion). If vasopressin is used, it must be given in conjunction with another vasopressor.*

   b) Respiratory Dysfunction is defined as the acute need for mechanical ventilation and **PaO2/FiO2 ratio of <250** (**or < 200** when the lung is the site of infection). For the

purposes of this protocol, mechanical ventilation is defined as any type of ventilation administered via an endotracheal tube or nasotracheal intubation. A simple administration of supplemental oxygen is NOT considered to be mechanical ventilation for the purposes of this study.

4) Subjects with coagulopathy characterized by an INR >1.40 without other known etiology (e.g., anticoagulant therapy, chronic liver disease)

5) Subjects with coagulopathy characterized by platelet count in the range of greater than (>) 30,000/mm^3 to less than (<) 150,000/mm^3 **OR** a greater than 30% decrease in platelets in 24 hours [23, 24, 25, 26, 27, 28].

Window 1 (≤ 24 hours):

Organ dysfunction (Section 2.6.1) and coagulopathy (Section 2.6.1) criteria need to be present **within 24 hours** of each other. The 24 hour window begins when a patient with suspected or confirmed bacterial infection develops either 1) sepsis associated organ dysfunction (cardiovascular or respiratory) or 2) first qualifying platelet result or first qualifying INR. The qualifying time for organ dysfunction and coagulopathy is as follows:

1. Sepsis associated organ dysfunction
    - Cardiovascular dysfunction: the time that vasopressors are initiated (Section 2.6.1, 3a).
        - For surgical patients having vasopressors initiated during surgery; if vasopressors are required post-surgery, the end time of the surgery is the qualifying time
    - Respiratory dysfunction: the time of intubation prior to the first qualifying PaO2/FiO2 ratio after intubation (Section 2.6.1, 3b).
        - For surgical patients that require mechanical ventilation for surgery: if the patient has a qualifying PaO2/FiO2 post-surgery due to sepsis associated respiratory dysfunction, the time the surgery ends is the qualifying time.

2. Coagulopathy

- Decreased platelets: a qualifying platelet count must occur within the 24 hour window (if more than one platelet is within the 24 hour window the time of the first qualifying platelet is to be used).
  - absolute value of > 30,000/ mm^3 and < 150,000/ mm^3.

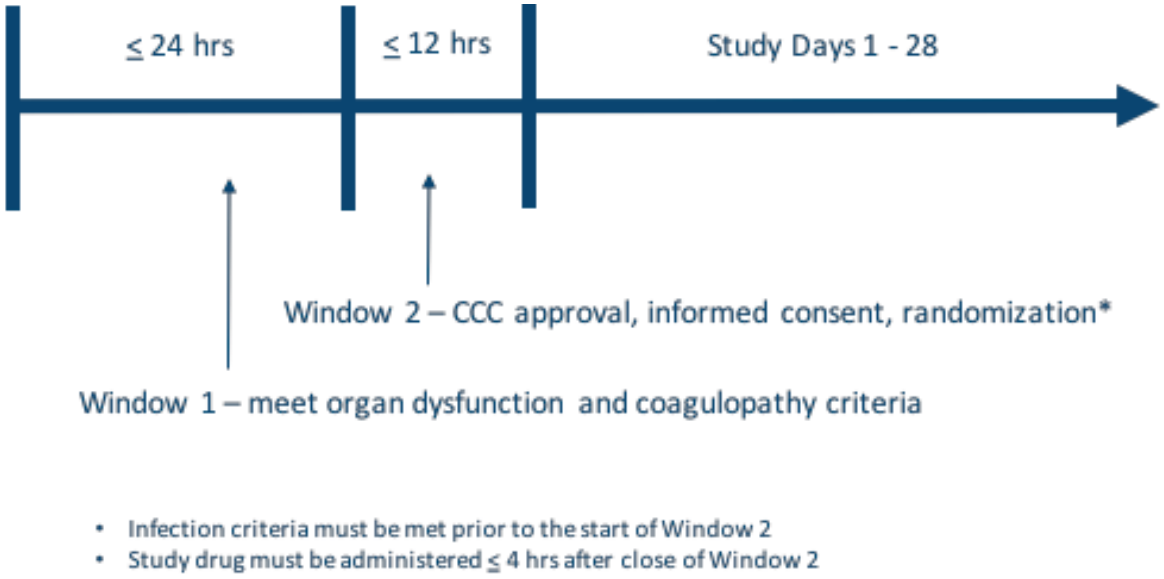
    OR
  - >30% decrease from one platelet count to another within 24 hours. (Patients with a platelet count of ≤ 30,000/ mm^3 are <u>not</u> eligible per Exclusion 10.)
- INR: first qualifying INR > 1.40

<u>Window 2 (≤ 12 hours):</u>

Window 2 is a 12 hour period of time that starts when the last inclusion criteria is met for sepsis-associated organ dysfunction and coagulopathy. During this window, eligibility must be confirmed, informed consent obtained, authorization to randomize obtained from the CCC, and the subject randomized.

Time windows and duration for the study are illustrated in Figure 1.

Figure 1 Enrollment Time Windows and Study Duration



Please note: Infection criteria needs to be met prior to the start of window 2. Once informed consent has been obtained and the CCC confirms that all study eligibility criteria have been met and provides authorization to randomize, the subject should be randomized even if the subsequent laboratory values (platelets and INR) show that the subject no longer meets eligibility criteria, assuming no other study exclusion criteria have emerged during this time period that disqualify the subject from being dosed with the study product. If a subject is transferred from another facility, Window 1 starts from the time a patient with suspected or confirmed bacterial infection develops either 1) sepsis associated organ dysfunction or 2) coagulopathy regardless of the facility. Once informed consent has been obtained and the CCC confirms that all study eligibility criteria have been met and provides authorization to randomize, the subject should be randomized. The first dose of study drug must be administered as soon as possible and no later than 4 hours after randomization. (Refer to **Section 13.2** Informed Consent for specific guidelines for Informed Consent).

2.6.2 Exclusion Criteria

*Candidates for the study will be excluded if **ANY** of the following criteria are present:*

1. Subject or Authorized Representative is unable or unwilling to provide initial or ongoing informed consent (as applicable per local and country regulations)
2. Subject is pregnant or breastfeeding or intends to get pregnant within 28 days of enrolling into the study
3. Subject is of childbearing potential and has a positive pregnancy test since admission to the hospital
4. Subject is < 18 years of age
5. Subject has a known allergy to ART-123 or any components of the drug product
6. Subject is unwilling to allow transfusion of blood or blood products
7. Presence of an advance directive to withhold life-sustaining treatment (patients not wishing to receive Cardiopulmonary Resuscitation (CPR) may qualify provided they receive all other resuscitative measures e.g. mechanical ventilation, vasoactive agents, cardioversion)
8. Subject has had previous treatment with ART-123
9. Body weight ≥ 175 kg

10. Platelets $\leq$ 30,000/ mm^3 for any reason, PT prolongation or thrombocytopenia that is not due to sepsis (e.g. AML or ALL in induction therapy, acute leukemia of the M3 type, myeloablative therapy within 4 weeks prior to enrollment, AIDS with persistent thrombocytopenia and/or bleeding disorder, ongoing pre-existing thrombocytopenia or coagulopathy).
11. Any surgery that is potentially hemorrhagic (e.g. intra-thoracic, intra-abdominal or non-traumatic orthopedic surgery of the femur or pelvis) that is completed within 12 hours prior to the first dose of study drug, or ongoing impairment of hemostasis as a result of one of these procedures (Refer to Section 2.6.3.)
12. A history of head trauma, spinal trauma, or other acute trauma with an increased risk of bleeding within 3 months prior to consent (subjects with minor head trauma may be enrolled if there is a normal neurological examination and a normal CT scan of the head/spine post injury documented in the medical record)
13. Cerebral Vascular Accident (CVA) within 3 months prior to consent
14. Any history of Intracerebral Arteriovenous Malformation (AVM), cerebral aneurysm, or mass lesions of the central nervous system
15. A history of congenital bleeding diatheses or anatomical anomaly that predisposes to hemorrhage (e.g. hemophilia, hereditary hemorrhagic telangiectasia)
16. Significant gastrointestinal bleeding (e.g., melena, hematemesis) within 6 weeks prior to consent unless a corrective interventional procedure has been performed (i.e., therapeutic endoscopy)
17. Subject is diagnosed with a known medical condition associated with a hypercoagulable state, including:
    a. Resistance to activated protein C or known Factor V Leiden
    b. Hereditary deficiency of protein C or protein S
    c. Presence of anticardiolipin antibody, antiphospholipid antibody, or prothrombin gene mutation
    d. Deep-vein thrombosis or pulmonary embolism within 3 months prior to consent (if evaluation is in progress, this should be completed before consideration for this trial)
    e. Any disorder with a requirement for full anticoagulation
18. History of cirrhosis or current Class C liver disease (Child-Pugh score of 10-15); (See Appendix E)

19. Portosystemic hypertension or known history of bleeding esophageal varices
20. History of solid organ, allogeneic bone marrow, or stem cell transplantation within the 6 months prior to consent (uncomplicated kidney and autologous stem cell/bone marrow transplant subjects may be enrolled at any time after they have recovered from their transplant procedure)
21. Acute pancreatitis where infection has not been documented by a positive blood or abdominal fluid culture or gram stain consistent with bacterial infection. Also, in the opinion of the treating physician the subject is at an increased risk for developing hemorrhagic pancreatitis over the duration of the study
22. Subjects with renal dysfunction defined as:
    a. Chronic renal failure requiring renal replacement therapy (RRT), or
    b. Acute renal failure with onset of oliguria (urine output < 0.3 ml/kg/hr) > 48 hours prior to first dose of study drug whether receiving RRT or not.
23. Use of anticoagulants, antiplatelet agents, antithrombotics and thrombolytics within the 72 hours prior to first dose of study drug with the exception of:
    a. Heparin locks/flushes
    b. DVT Prophylaxis (see Appendix G) per prophylactic dosing on the package insert as approved in your country.
    c. Up to 325 mg of aspirin daily for cardiac prophylaxis only
    d. Anticoagulants for RRT: Regional citrate is preferred (see Appendix G). It is recommended that if unfractionated heparin or LMWH is used, that the systemic exposure be less than or equal to the DVT prophylaxis dose allowed.
24. Life expectancy < 90 days due to underlying conditions such as, but not limited to, the following:
    a. Poorly controlled neoplasms
    b. New York Heart Association class IV or pulmonary vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform household duties), or chronic restrictive or obstructive pulmonary disease that also results in severe exercise restriction, or documented chronic hypoxia (needs continuous home oxygen treatment), hypercapnia, secondary polycythemia, severe pulmonary hypertension (Mean Arterial Pulmonary pressure level of > 40 mmHg) or respiratory dependency

c. Prior cardiac arrest requiring CPR without fully demonstrated neurological recovery, or subject with imminent death (in the next few hours)

d. End-stage neurological disorders (e.g., amyotrophic lateral sclerosis - Lou Gehrig's disease)

25. Current use of any chemotherapy agent likely to cause myeloablation (See Appendix H)
26. Participation in another research study involving an investigational agent within 30 days prior to consent or projected study participation during the 28 days post study randomization
27. Confirmed or suspected endocarditis

2.6.3 Post-surgical Subjects

For subjects that have had a potentially hemorrhagic surgery (e.g. intra-thoracic, intra-abdominal, or non-traumatic orthopedic surgery of the femur or pelvis) the first dose of study drug must not be administered within 12 hours post completion of major surgery.

2.7 Criteria for Discontinuation from Study Drug or Study Participation

2.7.1 Withdrawal from receiving study drug

A subject may remain in the study but discontinue the administration of study drug, at any time during treatment. Reasons may include:

1. Intolerable adverse event(s) such as Major Bleeding Event(s) **(Section 7.1)** or conditions that place the subject at high risk of bleeding.
2. Request by the subject or their AR / LAR.
3. Hospital discharge or transfer to another facility.
4. Investigator’s judgment (e.g. related SAE).
5. Administration of study drug is contraindicated if co-administration of an excluded concomitant medication (e.g. full heparinization, oral anticoagulant, anti-platelet drug) is required for subject treatment.
6. QTcB value of greater than 500 msec (provided that the baseline value was <500 msec) or the QTcB is >60 msec over baseline value and the subject is symptomatic.

Subjects who terminate study treatment prior to receiving the protocol specified 6 days of dosing will have ETT assessments performed 24 hours (±2 hours) after the last dose of study drug administration. In such cases, the subject will continue ongoing protocol specified evaluations through Day 28 and will be contacted at 3, 6 and 12 months for survival status. Approval for collection of this survival data will be provided at the time of the subject's original Informed Consent.

If the subject is discharged from the admitting hospital or transferred to another outside facility during the treatment phase (Days 1-6), the administration of the study drug will be discontinued at the time of the discharge or transfer. The ETT visit is completed prior to discharge.

If the subject is transferred from the admitting hospital ICU to another unit within the hospital, this is not considered as hospital discharge. Study drug administration, as well as all protocol specified study procedures, should continue uninterrupted.

2.7.2 Discontinuation from study participation

2.7.2.1 Discontinuation from study participation due to death

It is vital that all safety, concomitant medication(s), and health history data be collected and reported in accordance with all local and regional regulatory requirements as well as all Asahi Kasei Pharma America Corporation guidelines for any subject who expires while actively enrolled or during the follow up period after dosing is completed for this study. All study visit data from the time of informed consent to the time of death will be collected.

If a subject dies while on study, efforts will be made to determine the cause of death and collect information about the subject's status and treatments that he/she was receiving at the time of death. If available, a copy of the death certificate will be collected (in accordance with local regulations/statutes).

2.7.2.2 Discontinuation from study participation due to withdrawal of consent

Subjects may voluntarily discontinue participation in the study at any time, for any reason. During the initial informed consent process, Investigators should advise potential study subjects of their right to withdraw consent, and provide education regarding alternate treatment options that are available to them. In situations where consent for participation is obtained by an Authorized or Legally Authorized Representative (AR/LAR respectively) or an independent physician (as defined in **Section 13.2**), provisions for ongoing participation are at the discretion of the AR/LAR or an independent physician who maintains the same rights as outlined herein

for the study subject; until such time that the subject is deemed able to do so. Refer to **Section 13.2** Informed Consent for further guidelines.

If a subject indicates an interest in withdrawing from randomized treatment, Investigators should seek clarification about whether continued follow-up and survival status data collection subsequent to the subject's withdrawal is agreeable to the subject. This is covered when the initial Informed Consent is obtained. If such ongoing follow up is permissible, the subject should not be identified as having withdrawn consent.

At the time of withdrawal of consent, the subject should be reminded of their rights. All study visit procedures, as well as the End of Study (EOS) visit assessments should be completed up to the time that consent was withdrawn. The completion of all study visits up to the time that consent was withdrawn, as well as survival status at Day 28, 3 months, 6 months and 12 months post the first dose will be collected.

At the time of withdrawal of consent, final visit procedures and assessments will be performed unless the subject is unwilling to comply. The subject will be directed to follow up with their primary care physician for ongoing medical treatment, informed of any known options for medical care and will be provided information regarding who to contact for any questions as well as information about the outcome of the study once completed.

2.7.2.3 Discontinuation due to lost to follow up

Subjects who have not withdrawn consent, but have not returned for follow-up visits and no contact can be made to determine their status will be designated "Lost to Follow-up". Site personnel will designate a subject as Lost to Follow-up for the primary endpoint at Day 28 only after the subject or subject's representative has not responded to two documented attempts at telephone contact and a registered letter sent to the subject's last known mailing address. The Lost to Follow Up date will be recorded as the last date of contact with the subject. For all subjects who are lost to follow-up the investigator will report if, in the investigator's judgment, the subject was improving and likely to be alive on Day 28.

For subjects who have not withdrawn consent, site personnel are asked to make every attempt to collect long term survival status at the 3 month, 6 month and 12 month time points. Subjects are to be classified with a final status of "Lost to Follow Up" only if they are unable to be contacted at the 12 month survival status time point.

2.8 Data Monitoring Committee (DMC)

A DMC will monitor the progress of the study and review critical safety data. Membership will consist of a biostatistician and 2 clinicians in the field. The DMC will be independent of the study team and will have no direct involvement in other aspects of the trial. The DMC will follow operating procedures provided in the DMC Charter. A biostatistician, independent of the project team, will perform the statistical analyses, including interim analysis, for the DMC. This independent biostatistician will not be a member of the DMC. The DMC will review unblinded efficacy and safety data, including quality of study conduct measures. The DMC will provide recommendations to study leadership. DMC monitoring guidelines have been outlined in **Section 10.3** of this protocol.

The DMC will meet prior to study initiation and finalize the DMC Charter. Meetings may be held in-person or by teleconference. Interim Analyses will be held at predefined milestones formally throughout the study. In addition, the DMC can hold ad hoc meetings as deemed appropriate. Refer to **Section 12.3.1** for further information regarding the DMC.

2.9 Clinical Coordinating Centers (CCCs)

Two CCCs, Ocean State Clinical Coordinating Center (OSCCC) and St. Luc Clinical Coordinating Center (SLCCC), will be providing clinical support for study sites. These CCCs are comprised of experts in critical care, infectious disease and pulmonary medicine. The CCCs will work with the investigative sites to determine if subjects appropriately meet the study entry criteria and can be randomized into the study thereby ensuring an appropriate homogenous study population.

3 TREATMENTS

Subjects will be randomized to receive either ART-123 or Placebo via 1:1 randomization. After the subject is qualified for study entry, treatment assignment will be made via a Voice Activated or Web Access Automated Randomization System. ART-123 and Placebo are both supplied in 1 mL glass ampules, which must be maintained at 2°C–8°C and kept away from light during storage.

ART-123 or Placebo will be administered at a dose of 0.06 mg/kg/day up to a maximum dose of 6 mg/day, every 24 hours (plus or minus 2 hours) for six (6) consecutive days. When a subject requires a major surgery/intervention during the dosing period, if possible the surgery/intervention should be performed 12 hours after the last dose. If it is known ahead of

time that the subject will undergo major surgery/intervention, then the study drug dose that is due prior to the surgery should be held if the surgery/intervention is planned within the next 12 hours. Post procedure, the study drug is to be held for 12 hours and then may be resumed unless otherwise contraindicated. The study drug dosing clock now restarts, using the time the post procedure dose was given, and all subsequent doses are to be administered using the new clock. Subjects whose body weight is ≤100 kg will receive the study drug at a volume of 0.01 mL/kg/day (0.06 mg/kg/day) up to a volume of 1 mL/day (6mg). Subjects whose body weight in the range of 100-174 kg will receive 1 mL/day (6mg) of study drug regardless of body weight. A detailed rationale for the 0.06 mg/kg/day dose may be found in the Investigator's Brochure.

ART-123 or Placebo will be administered as an IV bolus injection or diluted in 50 mL of NS, and infused over a period of 15 minutes. ART-123 or Placebo must be given in a dedicated line and **must not** be administered concurrently with any other medications. If the same IV line that is used for delivery of other medications must be used for administering ART-123 or placebo **then the line must be flushed with at least 5 mL of 0.9% NS solution both prior to and following** the administration of ART-123 or placebo. If a heparin flush is requested it may be administered following the 0.9% NS flush, in accordance with institutional standards.

The study drug can be administered either via a central line or through a large bore (greater than or equal to 20-gauge) peripheral IV line. **Heparin coated central lines are not allowed for the administration of ART-123 or Placebo.**

After drawing up study drug from the ampule into the syringe, administration should occur as soon as possible post removal from the ampule.

3.1 Investigational Product, Dosage and Mode of Administration

3.1.1 ART-123 (thrombomodulin alpha)

ART-123 or Placebo, are administered at the equivalent dose of 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day for six days. ART-123 is given by intravenous bolus or rapid IV infusion, in which case 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day is diluted in 50 mL of NS and given over a period of 15 minutes. ART-123 must not be administered concurrently with any other medications or in the same IV line that is used for administering other medications. If the same IV line that is used for delivery of other medications must be used for administering study drug or placebo then the line must be flushed with at least 5 mL of 0.9% Saline solution both prior to and following of administration of study drug or placebo.

ART-123 is supplied as individual glass ampules containing 6.0 mg of formulated drug in 1 mL of total volume; with an overfill of 0.1mL. The total volume of each ampule equals 1.1 mL. Stability data show ART-123 is stable for up to 18 months when stored at 2°C–8°C. Photostability studies indicate that ART-123 is sensitive to light. The investigational drug product is kept in closed cartons and should be protected from sunlight at all times.

3.2 Reference Therapy, Dosage and Mode of Administration

3.2.1 Placebo for ART-123

Placebo for this study is supplied as identically labeled, individual glass ampules in 1 mL of total volume; with an overfill of 0.1mL. The total volume of each ampule equals 1.1 mL. Placebo will also be required to be maintained refrigerated at 2°C–8°C and protected from light during storage. Placebo must be administered according to the same procedures and guidelines as ART-123, i.e., Placebo must not be administered concurrently with any other medications and the IV line that is used for administering placebo must be flushed with at least 5 mL of 0.9% Saline solution both prior to and following administration of study drug or placebo.

3.3 Blinding

Study drug will be assigned and administered in a double blind fashion. In the event of a medical emergency where it is imperative to know which treatment arm the subject was randomized to in order to make future treatment decisions, the Investigator may break the blind for an individual subject.

Because there is no antidote for ART-123, and the treatment for subjects should be as per standard of care, there should be little reason for unblinding the treatment of an individual subject. If the Investigator needs to unblind an individual subject, the Medical Monitor or designee should be notified in advance whenever possible. In addition, the sponsor should also be notified prior to the blind being broken.

All adverse events causing the need for subject unblinding will be handled as a serious adverse event in accordance with the procedures outlined in this protocol. Any broken blind will need to be clearly justified, explained by a comment within the Electronic Case Report Form (eCRF), and captured on the Serious Adverse Event Form.

The treatment assignment for the subject can be determined by the Investigator only and only by calling into the automated system for randomization assignment via password protected access. The Investigator must record the date, time and the reason for the unblinding in the subject's study chart.

4 LABORATORY SAMPLES

For this study there will be both local and central laboratory blood draw requirements. The list below outlines which study specific laboratory blood draws are for central laboratory draws (using the provided central laboratory kit) and which are for local laboratory draws (using hospital stock supplies). If Standard of Care (SOC) local labs for Organ Dysfunction (OD) are to be drawn on the days where study drug is administered, we suggest these be drawn within 1 hour after the study drug is administered. On days where Standard of Care labs are drawn, use the PaO2/FiO2 (for ventilated subjects) results for the Organ Dysfunction assessments. If an ABG is not performed as SOC, a Pulse Oximetry O_2 saturation may be used for calculating the PaO2/FiO2 (Refer to **Appendix J: Conversions for PaO2/FiO2 calculations**). For centers that may be at an altitude of more than 1000 meters, an adjustment may be needed for purposes of calculating PaO2/FiO2.

To avoid contamination or clotting, all coagulation tests taken for the purposes of this study should be obtained from an original arterial stick or venipuncture. If it is not possible to obtain blood from an original stick or venipuncture, blood may be collected from an arterial line in which no Heparin is infused. The arterial line will be flushed with NS both prior to and after the blood draw. No coagulation samples can be obtained from a Heparin infused or Heparin coated central line. Heparin must not be used when flushing an arterial line for this purpose. The site staff should use proper collection technique as described in the Central Laboratory Manual. If an original arterial stick or venipuncture is used then to avoid clotting, the coagulation test tubes should not be the first tube of blood filled. Any other non-coagulation blood tests unable to be obtained from the original arterial stick or venipuncture may be taken from an existing port or line. If a central line is used, exploratory laboratory tests should be the last to be collected.

4.1 Central Laboratory Tests:

- Serum Chemistry profile (Sodium (Na), Potassium (K), Chloride (Cl), bicarbonate, non-fasting glucose (Glu), Calcium (Ca), Blood Urea Nitrogen (BUN), Creatinine, ALT, AST, Alkaline Phosphatase and total bilirubin)
- D-dimer
- Arterial lactate concentration
- Anti-drug & Neutralizing Antibodies to ART-123

- Plasma thrombomodulin concentration (PK)
- Exploratory Laboratory Tests
    - Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII
    - Inflammation: CRP, Microparticles, and C5a

4.2 Local Laboratory Tests:

- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Serum Chemistry (Creatinine, Total bilirubin at Baseline Visit only)
- Pregnancy test; Serum or Urine human Chorionic Gonadotropin (hCG) - Pregnancy test only required for woman of childbearing potential
- Platelet count
- Coagulation Panel (Prothrombin time and INR)
- Albumin and total bilirubin, if not performed as standard of care in the past 7 days (Screening), for Child-Pugh Score calculation in patients with severe liver disease.

5 VISIT SCHEDULE AND ASSESSMENTS

5.1 Screening Visit

Subjects must meet the 5 inclusion criteria (be in the ICU or acute care setting, infection, sepsis associated organ dysfunction, and coagulopathy) and have none of the exclusion criteria in order to be eligible for randomization in this study.

5.2 Consent and Randomization Process

Subjects who meet criteria for infection, sepsis-associated organ dysfunction and coagulopathy according to protocol parameters, are in an ICU or acute care setting, have none of the exclusion criteria, and have been consented, may be randomized after authorization to randomize has been provided by the CCC.

If in the opinion of the investigator the subject will require the administration of anticoagulants, antiplatelet agents, antithrombotics, or thrombolytics during any period of the study, that subject is not eligible for this study. A list of prohibited medications is provided in Appendix G**.** Subjects who discontinue dosing will follow the visit schedule and procedures as outlined in **Section 2.7.1** of this protocol. If the subject is female and is of childbearing potential, a pregnancy test (serum or urine hCG) will be obtained if not previously performed as SOC during this hospitalization, and the results determined and documented prior to baseline visit.

Guidelines for the management of subjects that require an AR/LAR or other legal intervention due to their medical status, and are unable to provide consent for him/herself, may be found in **Section 13.2**.

In extreme and urgent circumstances when emergent action is required to mitigate the risk of death and where allowable per local laws, it is understood that the presumed will of the subject will be determined by a physician and documented based on his/her knowledge of the study subject. As appropriate, an independent physician, who is a qualified medical doctor with at least one year's experience in intensive care medicine but must be from another department and/or hospital than the investigator, may sign the informed consent for the subject if the local laws, regulations and ethics committees approve this process. In countries where permissible, this independent physician may be from the same department. The study subject must be presented with the informed consent as soon as it is possible and reasonable, and informed consent obtained for continued study participation. The AR/LAR or independent physician may act as an agent on the subject's behalf once they are available to provide informed consent.

The above guidelines apply to all areas of the protocol where Informed Consent is referenced or required.

5.3 Baseline Visit (prior to dosing)

Subjects who meet all eligibility criteria and have signed informed consent will be discussed with the CCC for authorization to randomize. After the CCC verifies eligibility of the subject

and authorizes randomization, the subject will be randomized by the site via an automated phone/internet system.

Once the subject is randomized, the automated system will provide the study staff with a unique randomization number for the subject and an assigned investigational product kit number. The assigned kit should be ordered or obtained by the PI or designee from the pharmacy or applicable investigational product storage location.

For each study subject the following data/assessments are required to be collected:

The following data/assessments may have preceded the time of the last inclusion criteria and consent as the information is collected as part of the medical record. However, no data is collected until the subject has been consented.

- Demographics, height and weight (actual baseline dry weight since hospital admission or if unavailable, usual body weight. If weight is unavailable, estimated body weight can be used).
- Medical history (all known information regarding the subject's health history/relevant surgeries/interventions).
- Acute Physiology and Chronic Health Evaluation (APACHE) II[29,30] (timeframe for data collection is the 24 hours prior to the first dose, See Appendix K and Appendix L)
- Concomitant medications administered within the 7 days prior to randomization (including fluids for resuscitation and blood products).
- Historical information regarding treatment for the current episode of sepsis.
- Documentation of the infection (site of infection and, if available: positive culture results, prior antibiotics, sensitivity of cultured organism to antibiotics, nonmedical treatment such as surgery or drainage)
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- If Respiratory dysfunction: duration on mechanical ventilation, qualifying PaO2/FiO_2 ratio prior to randomization.
- If Cardiovascular Dysfunction: fluid administration, CVP, and/or PAWP, duration on vasopressors, name of vasopressor currently administered.
- If the subject is receiving dopamine, dobutamine, or other inotropes for cardiac dysfunction, record the dose.
- Record Interventions/Surgeries

The following assessments are to be performed/collected after the consent has been obtained, last inclusion criteria is met, and authorization to randomize has been received from the CCC:

- Vital signs: Pulse – beats per minute (BPM), Blood Pressure (BP) mmHg, Respirations – breaths per minute, Temperature
- Changes in concomitant medications
- Blood Product administration
- Physical Examination including the following: general appearance, Head, Eye, Ear Nose Throat (HEENT), neck, respiratory, cardiovascular, chest, abdomen, lymphatic, musculoskeletal and extremities, skin and neurologic examination
- 12 lead ECG: to be read centrally
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- Interventions/Surgeries
- Major Bleeding Events

Blood will be obtained for following local laboratory tests:

- Serum Chemistry (Creatinine and Total bilirubin)
- PaO2/FiO2 (only for respiratory dysfunction)
- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Platelet count
- Coagulation Panel (Prothrombin time and INR)

Additional labs will be drawn for analysis at the central laboratory:

- Serum Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase and Total bilirubin)
- D-dimer
- Plasma thrombomodulin concentration (PK)
- Exploratory Laboratory Tests
    - Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII

- Inflammation: CRP, Microparticles, and C5a
- Arterial lactate concentration
- Anti-drug Antibodies to ART-123

For randomized subjects who do not receive any study drug all study tests completed prior to the point it was known the subject would not be dosed will be collected. All AEs, SAEs and survival status through Day 28 will be collected, but further study visits/procedures (including ETT) will not be performed.

5.4 Dosing Visit (Day 1)

The first dose of study drug must be administered as soon as possible and within 4 hours after randomization. For post-surgical subjects see Section 2.6.3. Follow the instructions in the Drug Accountability and Handling Manual for proper preparation and administration instructions.

Within one hour after the administration of the first dose record the following:

- Vital signs
- Changes in concomitant medications
- Blood Product administration
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- PaO2/FiO2 if available within one hour after IP administration (only if vented)
- Interventions or Surgeries
- Major Bleeding Events
- Assessment of the degree of burden and risk threshold, and assess continuation of treatment with ART-123/placebo (refer to **Section 7.5**)

5.5 Day 2 Visit

On Day 2, administration of the second dose of study medication will begin 24 hours (±2 hours) after the first dose was given (dosing Day 1). Please refer to **Section 3** if the subject has had an intervention/procedure since the first dose of study drug.

Within one (1) hour after study drug administration, perform/record the following:

- Vital signs
- Changes in concomitant medications
- Blood product administration
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- Interventions/Surgeries
- Major Bleeding Events
- Assessment of the degree of burden and risk threshold, and assess continuation of treatment with ART-123/placebo (refer to **Section 7.5**)

Blood will be obtained for following local laboratory tests:

- PaO2/FiO2 (only if vented and not collected as SOC)
- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Platelet count
- Coagulation Panel: Prothrombin time and INR

Additional blood samples will be drawn for analysis at the central lab:

- Serum Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase and Total bilirubin)
- D-dimer

5.6 Day 3 Visit (Pre-dose)

On Day 3, administration of the third dose of study medication will begin 48 hours (±2 hours) after the first dose of study medication was given (Dosing Day 1). Please refer to **Section 3** if the subject has had an intervention/procedure since the first dose of study drug.

Within one (1) hour PRIOR to study drug administration, blood samples will be collected for the following central laboratory tests:

- Plasma thrombomodulin concentration (PK)

- Exploratory Laboratory Tests
    - Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII
    - Inflammation: CRP, Microparticles, and C5a

5.7 Day 3 Visit (Post-dose)

Within one (1) hour after study drug administration, perform/record the following:

- Vital signs
- Changes in concomitant medications
- Blood product administration
- 12 lead ECG: to be read centrally
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- Interventions/Surgeries
- Major Bleeding Events
- Assessment of the degree of burden and risk threshold, and assess continuation of treatment with ART-123/placebo (refer to **Section 7.5**)

Blood will be obtained for following local laboratory tests:

- PaO2/FiO2 (only if vented and not collected as SOC)
- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Platelet count
- Coagulation Panel (Prothrombin time and INR)

Additional labs will be drawn for analysis at the central lab:

- Serum Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase and Total bilirubin)
- D-dimer
- Plasma thrombomodulin concentration (PK)

- Exploratory Laboratory Tests
    - Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII
    - Inflammation: CRP, Microparticles, and C5a

5.8 Days 4-6 Visits

On Days 4, 5 and 6 administration of the fourth, fifth and sixth doses of study medication will begin 72, 96 and 120 hours (±2 hours) after the first dose of study drug was administered, respectively. Please refer to **Section 3** if the subject has had an intervention/procedure since the first dose of study drug.

Within one (1) hour after the administration of study drug (doses 4-6), perform/record the following:

- Vital Signs
- Changes in concomitant medications
- Blood product administration
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- Interventions/Surgeries
- Major Bleeding Events
- Assessment of the degree of burden and risk threshold, and assess continuation of treatment with ART-123/placebo (refer to **Section 7.5**)

Blood will be obtained for the following local laboratory tests on Days 4 and 6 only:

- PaO2/FiO2 (only if vented and not collected as SOC)
- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Platelet count
- Coagulation Panel (Prothrombin time and INR)

Additional labs on Days 4 and 6 only will be drawn for analysis at the central laboratory:

- Serum Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase and Total bilirubin)
- D-dimer

On study Day 5 only, blood will be obtained for the following local laboratory test:

- PaO2/FiO2 (only if vented and not collected as SOC)

On study Day 6 only, the following will be performed:

- 12 lead ECG: to be read centrally
- Blood will be will be drawn for analysis at the central laboratory:
  - Plasma thrombomodulin concentration (PK)
  - Exploratory Laboratory Tests
    - Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII
    - Inflammation: CRP, Microparticles, and C5a

Days 4-6

If the QTcB is >500 msec or the QTcB is > 60 msec over the baseline value, continue to monitor ECGs once daily until the earlier of Day 14 or the time when such conditions are no longer met. In the event of hospital discharge at this time, the Investigator should carefully evaluate these parameters prior to hospital discharge.

5.9 Day 7 Visit

On Day 7, assessments will begin 144 hours (± 2 hours) after the first dose (dosing Day 1) of study drug was administered. If a subject is discharged on Day 7, the Day 7 Visit, not the Hospital Discharge Visit, is performed.

Perform/record the following:

- Vital Signs
- Changes in concomitant medications
- Blood product administration
- 12 lead ECG: to be read centrally
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization

- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- Interventions/Surgeries
- Major Bleeding Events

Blood will be obtained for following local laboratory tests:

- PaO2/FiO2 (only if vented and not collected as SOC)
- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Platelet count
- Coagulation Panel (Prothrombin time and INR)

Additional blood samples will be drawn for analysis at the central laboratory:

- Serum Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase and Total bilirubin)
- D-dimer
- Plasma thrombomodulin concentration (PK)
- Exploratory Laboratory Tests
    - Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII
    - Inflammation: CRP, Microparticles, and C5a
- Arterial lactate concentration

If the QTcB is >500 msec or the QTcB is > 60 msec over the baseline value, continue to monitor ECGs once daily until the earlier of Day 14 or the time when such conditions are no longer met. In the event of hospital discharge at this time, the Investigator should carefully evaluate these parameters prior to hospital discharge.

5.10 Early Treatment Termination (ETT) Visit

The ETT visit is for subjects who discontinue study drug treatment early and remain hospitalized or who are discharged from the hospital on Study Days 1-6. The ETT Visit assessments are to be done in place of the daily assessments required for the actual study visit day.

- For subjects who discontinue treatment early (prior to the 6th dose) and remain hospitalized: the ETT is performed 24 hours (±2 hours) after the last dose of study medication that was administered.
- For subjects discharged from the hospital on Study Days 1-6: the ETT is performed (not the Hospital Discharge Visit),

Note: Any subject who completes the ETT visit remains in the study. If the subject is still hospitalized, study visits must continue to be completed. All subjects discharged from the hospital before Day 14 must return for Day 14 and Day 28 visit procedures. Subjects discharged from the hospital after Day 14 but before Day 28 must return for Day 28 procedures. All subjects must be contacted at 3, 6 and 12 months for survival status.

Record the following:

- Vital Signs
- Changes in concomitant medications
- Blood product administration
- 12 lead ECG: to be read centrally
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- Interventions/Surgeries
- Major Bleeding Events

Blood samples will be obtained for following local laboratory tests:

- PaO2/FiO2 (only if vented and not collected as SOC)
- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Platelet count
- Coagulation Panel (Prothrombin time and INR)

Additional blood samples will be drawn for analysis at the central lab:

- Serum Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase and Total bilirubin)

- D-dimer
- Plasma thrombomodulin concentration (PK)
- Exploratory Laboratory Tests
    - Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII
    - Inflammation: CRP, Microparticles, and C5a
- Arterial lactate concentration

If the QTcB is >500 msec or the QTcB is > 60 msec over the baseline value, continue to monitor ECGs once daily until the earlier of Day 14 or the time when such conditions are no longer met. In the event of hospital discharge at this time, the Investigator should carefully evaluate these parameters prior to hospital discharge.

5.11 Days 8-13

Beginning with Day 8 all prospective visits are based on calendar days. From this visit forward days are calendar days and are counted as follows: first dose on Day 1=1, D2=2, etc.

On study days 8-13, the following assessments will be completed as long as the subject remains in the hospital:

Perform/record the following:

- Changes in concomitant medications
- Blood product administration
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis and if the subject is vented, collect blood for PaO2/FiO2 (if not done as SOC)
- Interventions/Surgeries
- Major Bleeding Events

If the QTcB is >500 msec or the QTcB is > 60 msec over the baseline value, continue to monitor ECGs once daily until the earlier of Day 14 or the time when such conditions are no longer met. In the event of hospital discharge at this time, the Investigator should carefully evaluate these parameters prior to hospital discharge.

5.12 Day 14 (+ 3 days)

Subjects must return to the hospital for Day 14 procedures (+3 day deviation is acceptable). For subjects who remain hospitalized, this visit's procedures are performed on Day 14. If a subject is to be discharged on Day 13, the Day 14 Visit procedures must be performed in lieu of the procedures scheduled for Day 13. Subjects who are discharged from the hospital on the same day as the Day 14 Visit, complete the Day 14 Visit not the Hospital Discharge Visit.

Perform/record the following:

- Vital signs
- Changes in concomitant medications
- Blood product administration
- 12 lead ECG: to be read centrally
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- Interventions/Surgeries
- Major Bleeding Events

Blood will be obtained for following local laboratory tests:

- PaO2/FiO2 (only if vented and not collected as SOC)
- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Platelet count
- Coagulation Panel (Prothrombin time and INR)

Additional blood samples will be drawn for analysis at the central laboratory:

- Serum Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase and Total bilirubin)
- D-dimer
- Plasma thrombomodulin concentration (PK)
- Exploratory Laboratory Tests
    - Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII

- Inflammation: CRP, Microparticles, and C5a

- Anti-drug antibodies to ART-123

5.13 Days 15-27

On study days 15-27, the following assessments will be completed as long as the subject remains in the hospital:

Perform/record the following:

- Changes in concomitant medications
- Blood product administration
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis and if the subject is vented, collect blood for PaO2/FiO2 (if not done as SOC)
- Interventions/Surgeries
- Major Bleeding Events

5.14 Hospital Discharge

This visit applies to subjects discharged from the hospital on Day 8 up to Day 28 except for Days 13 / 14 or Day 28 in which case please refer to the respective study visit for study procedures.

Perform/record the following prior to discharge:

- Vital signs
- Changes in concomitant medications
- Blood product administration
- 12 lead ECG: to be read centrally

  Note: If the QTcB is >500 msec or the QTcB is > 60 msec over the baseline value, continue to monitor ECGs once daily until the earlier of Day 14 or the time when such conditions are no longer met. In the event of hospital discharge at this time, the

Investigator should carefully evaluate these parameters prior to hospital discharge. Upon meeting this condition, the Hospital Discharge Visit is to be performed.

- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- Interventions/Surgeries
- Major Bleeding Events

Blood will be obtained for following local laboratory tests:

- PaO2/FiO2 (only if vented and not collected as SOC)
- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Platelet count
- Coagulation Panel (Prothrombin time and INR)

Additional labs will be drawn for analysis at the central lab:

- Serum Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase, and Total bilirubin)
- D-dimer
- Plasma thrombomodulin concentration (PK)
- Exploratory Laboratory Tests
    - Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII
    - Inflammation: CRP, Microparticles, and C5a
- Anti-drug antibodies to ART-123

All subjects discharged from the hospital before Day 14 must return for Day 14 and Day 28 visit procedures. Subjects discharged from the hospital after Day 14 but before Day 28 must return for Day 28 procedures.

All subjects must be contacted at 3, 6 and 12 months for survival status.

5.15 Day 28 (+3 days) or End of Study Visit

For subjects who remain hospitalized, assessments will be performed on the 28th day using the first dosing day as Day 1. Subjects who were discharged must return to the hospital for this visit so safety assessments can be performed. For subjects who were discharged from the hospital prior to Day 28, there is a visit window of +3 days and the subject must return on Day 28–31 for the completion of this visit. If a subject is unable or unwilling to return to the hospital for this visit, it may be conducted via telephone and any required assessments that cannot be done will be recorded as protocol deviations (i.e., laboratory draws). Telephone based assessments will document the date of the call, the name of the person initiating the call, the name and relationship to the subject of the person providing the information if the subject is unable to do so, and the survival status of the subject. Additionally, the subject/person providing the information will be asked about any potential adverse events, significant bleeding inclusive of any major bleeding events, or re-hospitalizations that the subject may have had since their discharge date and any changes to medications they are taking.

The End of Study Visit occurs whenever the subject discontinues study participation (as defined in **Section 2.7.2.2**) from the **study** prior to Day 28.

Perform/record the following:

- Changes in concomitant medications
- Blood product administration
- Adverse Events/Serious Adverse Events
- Assessment of ICU stay and hospitalization
- Complete the Organ Dysfunction (OD) assessments of Shock, Ventilator, Dialysis
- Interventions/Surgeries
- Major Bleeding Events

Blood will be obtained for following local laboratory tests:

- PaO2/FiO2 (only if vented and not collected as SOC)
- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Platelet count
- Coagulation Panel (Prothrombin time and INR)

Additional blood samples will be drawn for analysis at the central laboratory:

- Serum Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase and Total bilirubin)
- Anti-drug antibodies to ART-123. Additionally, all subjects that develop anti-drug antibodies to ART-123 will be followed for blood draw and medical evaluation at 3 months intervals until their serum antibody titer results become negative for a maximum duration of 18 months. Serum samples from subjects that have demonstrated the development of antidrug antibodies that are present on Day 28 or End of Study Visit will be tested for the presence of neutralizing antibodies.

Note: Survival status for all subjects must be reflective of survival status on calendar Day 29.

5.16 Survival Status at Day 28 (+3 day) Visit

Please note that survival status must reflect subject status on or after the 29th calendar day, which is 28 days after the administration of the first dose of the study drug. If subject has died, additional information required includes:

- Date of Death
- Cause of Death (including Death Certificate and autopsy results if available)

5.17 3 Month, 6 Month and 12 Month Follow-Up Visits

Subjects will be contacted to obtain their survival status at 3 months (90 ± 3 Days), 6 months (180 ± 3 Days) and 12 months (360 ± 3 days) post the first dose of study drug. This information can be obtained via telephone or in person. All reasonable efforts must be made to obtain the actual survival status for the subject. At a minimum, there must be 2 documented telephone calls to the subject's last known telephone number and a certified letter sent to their last known address. If a subject cannot be located at 3 months, the same attempts must be made at 6 months and 12 months respectively. Subjects will only be considered lost to follow up if they cannot be located at 12 months post study completion.

5.18 Follow-Up Visits for Subjects who have an anti-ART-123 antibody

Any subject with positive anti-ART-123 antibody results will return to the site at 3 month intervals for collection of a blood sample to be used for determination of presence or absence

of the antibody. Serum samples from subjects that have demonstrated the development of antidrug antibodies that are present on Day 28 or at the "End of Study" Visit will be tested for the presence of neutralizing antibodies.

This process will be continued every 3 months until antibody results are negative or until the subject's 18 month Follow-Up Visit. Sites will be informed when subjects are antibody positive.

SAEs/thrombotic events information in these antibody positive subjects will be collected and reported to the sponsor over a maximum of 18 months or subject becoming antibody negative, whichever is earlier.

5.19 Schedule of Activities

Table 1: Visit Schedule and Assessments

Assessment Period	Screen-ing	Base-line	Dosing							Post Treatment Follow-up							Long Term FU		
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ETT/ LD24	V11	V12	V13	HD	V14	FU 3m	FU 6m	FU 12m
Study Day		0	1[3]	2[3]	Day 3 Pre	Day 3 Post[3]	4[3]	5[3]	6[3]	7[6]	ETT Last Dose 24 ± 2 hrs[b]	8-13[1, 9]	14 (+3d)[1]	15-27[9]	Hospital Discharge[12]	28 (+3d)/ EOS[a,8]	3 m (90±3 d)	6 m (180±3 d)	12 m (360±3 d)
Informed Consent	X																		
Inclusion/Exclusion Criteria	X																		
Pregnancy Test (serum/urine)	X																		
Platelet, WBC w/ diff and INR (LOCAL laboratory draw)	X																		
Verification of Eligibility (CCC)		X																	
Randomization		X																	
Demographics, Height/Weight		X																	
Medical History and APACHE II		X																	
Vital Signs (Pulse, BP, Respirations, Temperature)		X	X	X		X	X	X	X	X	X		X		X				
Record Con. Med. /Blood Product Admin.		X	X	X		X	X	X	X	X	X	X	X	X	X	X			
Treatment Given for Current Episode of Sepsis		X																	
Documentation of Infection		X																	
Physical Examination		X																	
12 Lead Central ECG[9]		X				X	**Q**[5]	**Q**[5]	X[5]	X[5]	X[5]	**Q**[5]	X[5]		X[5]				
Assessment of AE/SAE		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X[10]	X[10]	X[10]
ICU Stay and Hospitalization Assessments		X	X	X		X	X	X	X	X	X	X	X	X	X	X			

Assessment Period	Screen-ing	Base-line	Dosing							Post Treatment Follow-up							Long Term FU		
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ETT/ LD24	V11	V12	V13	HD	V14	FU 3m	FU 6m	FU 12m
Study Day		0	1[3]	2[3]	Day 3 Pre	Day 3 Post[3]	4[3]	5[3]	6[3]	7[6]	ETT Last Dose 24 ± 2 hrs[b]	8-13[1, 9]	14 (+3d)[1]	15-27[9]	Hospit-al Discha-rge (HD)[12]	28 (+3d)/ EOS[a,8]	3 m (90±3 d)	6 m (180±3 d)	12 m (360±3 d)
Organ Dysfunction Assessments (Shock, Ventilator, Dialysis)		X	X	X		X	X	X	X	X	X	X	X	X	X	X			
LOCAL LABORATORY:																			
Organ Dysfunction Assessments, total bilirubin & serum creatinine		X																	
Organ Dysfunction Assessments, PaO2/FiO2 if vented (use SOC laboratory, if available)		X	X[7]	X		X	X	X	X	X	X	X	X	X	X	X			
CBC w/differential, Platelets, Coagulation (PT/INR)		X		X		X	**X**		**X**	X	X		X		X	X			
CENTRAL LABORATORY																			
Serum Chemistry		X		X		**X**	**X**		**X**	X	X		X		X	X			
D-dimer		X		X		**X**	**X**		**X**	X	X		X		X				
Plasma PK, Exploratory Labs		X			**X[4]**	**X**			**X**	X	X		X		X				
Arterial lactate		X								X	X								
Anti-ART-123 Antibodies		X											X		X	X[10]	X[10]	X[10]	X[10]
Interventions / Surgeries		X	X	X		X	X	X	X	X	X	X	X	X	X	X			
Major Bleeding Events		X	X	X		X	X	X	X	X	X	X	X	X	X	X			
Assessment of the degree of burden and risk threshold, and assess continuation of treatment with ART-123/placebo			X	X		X	X	X	X										
Dispense ART-123/Placebo[2]			X	X		X	X	X	X										
Survival Status																X	X	X	X

Table Footnotes:

a EOS = End of Study – When a subject is discontinued from the study prior to Day 28 for any reason other than Death (i.e., withdrawal of consent as defined in **Section 2.7.2**). This does not include the subjects who discontinue study drug early, but remain in the study for all other assessments.

b This visit is performed when a subject is discharged from the hospital on Study Days 1-6 or when a subject remains hospitalized and discontinues study drug administration prior to the 6th dose. The Early Treatment Termination Visit is performed 24 hours (± 2 hours) after the last dose of study medication if study drug administration was discontinued early or this window does not apply. This visit is done in place of the daily study visit.

1. If the subject is to be discharged from the hospital on Day 13 perform the Day 14 visit in place of Day 13 visit (Hospital Discharge visit is not performed). ONLY if subject has been discharged from the hospital is there a +3 day window for the subject to return for the Day 14 assessments and labs. Subjects who remain hospitalized for Day 14 must have the assessments performed on the 14th calendar day.
2. **The first dose of study drug must be administered as soon as possible after randomization and within 4 hours**. **For post-surgical patients that had potentially hemorrhagic surgery the first dose of study drug must not be administered within 12 hours of major surgery.** (See Section 2.6.3.) **All dosing times are based on the first dose of drug. The windows are: Day 2: 24 hours (±2 hours), Day 3: 48 hours (±2 hours), Day 4: 72 (±2 hours), Day 5: 96 hours (±2 hours) and Day 6: 120 hours (±2 hours). If IP is held due to surgery refer to Section 3.** Dosing is discontinued when a subject is discharged from the hospital. Administration of study drug is contraindicated if the co-administration of excluded concomitant medication (e.g. full heparinization, oral anticoagulant, anti-platelets drug) is required for subject treatment, or has an intolerable adverse event, such as bleeding events or conditions that place the subject at high risk of bleeding.
3. Assessments are made within one hour after IP administration on Dosing Days. If blood samples (central, local and Arterial Blood Gas if vented, and not performed as SOC) and ECG are required these are to be completed within (1) hour AFTER study drug administration.
4. **Within one (1) hour PRIOR to study drug administration, blood samples will be collected.**
5. **"Q" ECGs** If the QTcB is > 500 msec or the QTcB is >60 msec over the baseline value, the Investigator should evaluate the subject prior to hospital discharge. If the subject remains hospitalized, continue to monitor ECGs once daily until the earlier of Day 14 or the time when such conditions are no longer met. Use the QTcB from the ECG printout obtained during the study visit for these assessments.
6. On Day 7, assessments will begin 144 hours (± 2 hours) after the first dose (dosing Day 1) of study drug was administered. If the subject is discharged on Day 7, complete the Day 7 visit (not Hospital Discharge Visit).
7. **On Day 1 record Arterial Blood Gas only if performed within one hour after IP administration.**
8. The End of Study Visit occurs whenever the subject discontinues study participation (as defined in **Section 2.7.2**) prior to Day 28. ONLY if subject has been discharged is there a +3 day window for the subject to return to the hospital for Day 28 assessments and labs. Subjects who remain hospitalized on Day 28 must have the assessments performed on the 28th calendar day. (Day 1 is the day of administration of the first dose of study drug.) Survival Status is to reflect survival status on Day 29. If a subject is unable or unwilling to return to the hospital for this visit, information may be collected via telephone. Any required assessments that cannot be done will be recorded as protocol deviations (i.e., laboratory draws).
9. Beginning with Day 8 all prospective visits are based on calendar days. On study days 8-13 and 15-27, assessments are completed as long as the subject remains in the hospital.
10. Only subjects that develop anti-drug antibodies to ART-123 will be followed for blood draw and medical evaluation at 3 months intervals until their serum antibody titer results become negative for a maximum duration of 18 months. Subjects who return for testing will be queried for occurrence of any SAEs and clinical evidence of thrombosis.
11. 3 Month, 6 Month and 12 Month Follow up: Subjects will be contacted to obtain their survival status at 3 months (90±3 Days), 6 months (180±3 Days) and 12 months (360±3 days). If a subject cannot be located at 3 months, the same attempts must be made at 6 months and 12 months respectively. Subjects will only be considered lost to follow up if they cannot be located at 12 months post study completion.
12. Hospital Discharge (HD) visit applies only to subjects who are discharged from the hospital on Study Day 8 onwards (except for subjects who are discharged on Days 13/14 or Day 28).

6 EFFICACY ASSESSMENTS

Primary Efficacy Endpoint:

- 28 day all-cause mortality

Secondary Efficacy Endpoints:

- Follow-up of all-cause mortality at 3 months
- Resolution of organ dysfunction through Day 28 as measured by:
    - Shock free and alive days
    - Ventilator free and alive days
    - Dialysis free and alive days

Tertiary Efficacy Endpoints:

- Follow-up of all-cause mortality at 6 and 12 months
- Organ Dysfunction (Hepatic, Renal, Respiratory and Cardiac (Septic Shock) at Baseline, Day 3, Day 7, Day 14 and Day 28; Hepatic Dysfunction and Renal Dysfunction will be assessed with central laboratory data (total bilirubin and serum creatinine, respectively)
- ICU free and alive days through Day 28
- Hospitalization free and alive days through Day 28
- INR at Baseline, Day 3, Day 7, Day 14 and Day 28

7 SAFETY ASSESSMENTS AND REPORTING

7.1 Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. A baseline event refers to medical history that is present prior to the last inclusion criteria being met and obtaining informed consent. Examples of adverse events include:

- Increase in severity of a baseline event

- Clinically significant worsening of laboratory values post baseline (consolidate to a diagnosis if available)
- A new event with an onset date post baseline
- An event present at baseline where more aggressive treatment or an intervention/surgery is required post baseline (e.g. increase in total dosage per day, an invasive intervention such as chest tube insertion, debridement, etc.).

All local and systemic adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through other means, will be collected and recorded on the Adverse Event form and followed as appropriate.

Once the patient is authorized to randomize SAEs will be collected through Day 28. Once randomization has occurred both AEs and SAEs are collected. The DAIDS Toxicity/Adverse Event Grading Table (Appendix I) will be used by the Investigators to grade the events in the Case Report Form. If Appendix I does not provide severity guidelines for certain events, please see **Section 7.1.1** of the protocol.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology by the data management group.

Medical conditions/diseases present before authorization to randomize are only considered AEs if they subsequently worsen in severity, require more aggressive treatment/intervention/surgery, or if they resolve then re-emerge. Whenever possible, a diagnosis will be used to describe the AE. If a diagnosis is not available, the event will be captured using signs and symptoms. Each sign or symptom is its own AE until a diagnosis that they can be collapsed under is known.

Clinically significant laboratory abnormalities (both from central or local laboratories), if not part of a diagnosis, are required to be captured as AEs.

As far as possible, each AE will also be described by:

- The duration (start and end dates)
- The severity grade (Grade 1/mild, Grade 2/moderate, Grade 3/severe, Grade 4/Potentially life threatening as defined by the DAIDS Toxicity Table)
- The relationship to the study drug (none, unlikely, related)
- Whether the AE involved bleeding of any kind
- The action(s) taken
- The outcome

Major Bleeding Events

A Major Bleeding event is defined as:

- any intracranial hemorrhage,
- any life-threatening bleeding,
- any bleeding event classified as serious by the Investigator (e.g., resulting in permanent morbidity),
- the administration of at least 1440 mL (typically 6 units) of packed red cells over two consecutive days.[6]

Note: Should a major bleeding event occur, study product must be discontinued.

All major bleeding events must be collected, documented, and promptly reported as SAEs.

Blood product administration will be recorded in the eCRF.

7.1.1 Severity of Adverse Events

The Investigator is to classify the severity of an AE using the DAIDS Toxicity Table provided in Appendix I. If the toxicity table does not provide severity guidelines for certain events, the following definitions will be used:

Table 2: **Guidelines for Grading AE Severity**

Severity	**Characteristic**
Mild:	Symptoms causing no or minimal interference with usual social & functional activities
Moderate:	Symptoms causing greater than minimal interference with usual social & functional activities
Severe:	Symptoms causing inability to perform usual social & functional activities
Potentially Life-Threatening	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in **Section 7.2.** An AE of severe intensity need not

necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

If an adverse event changes in severity, the worst severity of the AE should be recorded. Should the AE become serious, the AE record will note an end date and a new entry for the SAE should be recorded with an onset date equal to the date the event met seriousness criteria.

7.1.2 Relationship of AE to Study Drug

The following table should be used as a guideline for assigning the relationship of the adverse event to the study drug.

Table 3: Guidelines for Grading Relationship of AE to Study Drug

Association	Definition
None (not related):	(1) The existence of a clear alternative explanation (e.g., mechanical bleeding at surgical site) or (2) non-plausibility, e.g., the subject is struck by an automobile or cancer developing a few days after drug administration.
Unlikely (remote):	A clinical event, including laboratory test abnormality (if applicable), with an improbable time sequence to drug administration and in which other drugs, chemicals, or underlying disease provide plausible explanations.
Related:	A clinical event, including laboratory test abnormality (if applicable), occurring in a reasonable time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.

Adverse events judged as “Unlikely” or “Related” will be defined as “Adverse Drug Reaction”.

7.2 Serious Adverse Events

Information about all serious adverse events (SAEs) must be collected and recorded on the SAE Report form and faxed or emailed to the sponsor within 24 hours of learning of its occurrence.

If follow-up indicates a change in the SAE from serious to fatal or life-threatening, this information needs to be reported within 24 hours. If a non-serious AE becomes serious, this and other relevant follow-up information must also be reported within 24 hours as described above.

(Safety reporting contact information is provided in Appendix A). The site is to follow their local regulations related to the reporting of SAEs to their local IRB/REB/IEC. An SAE is any undesirable sign, symptom, or medical condition which:

- Is fatal or life-threatening (i.e., an event with an outcome of 'Death'), or
- Requires or prolongs inpatient hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Constitutes a congenital anomaly or a birth defect; or
- Is medically significant, as determined by a qualified health professional, may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above
- Major Bleeding Events must be reported as SAEs (**See Section 7.1**)
- Any adverse event causing a need for unblinding must be reported as a serious adverse event

Events **not** considered to be SAEs are:

- Hospitalizations for treatment which is elective or pre-planned, for a pre-existing condition that did not worsen; or
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission.

All on-study deaths, including new fatal adverse events or adverse events that worsen post-baseline resulting in death, must be reported as the outcome of an associated SAE. If the cause of death is not immediately known the event may be reported initially as "Death", with the actual diagnostic event term provided as follow-up as soon as it is determined.

Pregnancies are not considered SAEs unless complications result which meet serious criteria. Pregnancy, although not in itself an SAE, must also be reported to the Sponsor within 24 hours of becoming aware on the Pregnancy Report Form, using the contact information provided in Appendix A. Pregnancies will be followed to term in order to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

All SAEs which occur after the subject has been authorized for randomization will be reported. SAEs are collected through Day 28 and followed until resolution or final outcome. AEs will be collected after authorization for randomization through Day 28, for those subjects that are randomized.

Any subject with positive anti-ART-123 antibody results will have SAEs/thrombotic events captured beyond Day 28 until antibody results are negative or until the subject's 18 month Follow-Up Visit. Clinical evidence of thrombosis may include deep vein thrombosis (DVT), pulmonary embolism, post-thrombotic syndrome, superficial thrombophlebitis, stroke, and myocardial infarction.

Sites will be informed when subjects are antibody positive, after which SAEs and thrombotic events occurring after Day 28 be collected and reported.

7.3 Expected Adverse Events

Expected Adverse Events are those that are consistent with the current version of the Investigator Brochure, including specificity or severity.

7.4 Expedited Reporting

All serious adverse events meeting the definition of reportable will be forwarded to the proper governing regulatory authority within the mandated timelines set forth by that agency.

Once the safety report has been generated and forwarded to the proper agency, a letter will be written and forwarded to the study Investigators. The Investigators will be instructed to submit this notification to their IRB/REB/IEC as soon as possible according to their local requirements.

7.5 Assessment of Risk Burden

In acknowledgement of the need to provide added oversight for vulnerable populations, monitoring for the degree of burden and risk, and assessment of the appropriateness of continuation of treatment with ART-123/placebo during the dosing period of Days 1-6 will be performed. Since the sepsis subjects enrolled to this study have critically ill conditions at the entry, definitive thresholds based on laboratory assessments or physical examination cannot be defined, and the risk and burden for a subject should be monitored by referring to all the assessments and examinations required for this protocol as well as performed as a standard of care. Additionally, because of the inherent risk of bleeding with compounds such as ART-123, in addition to the assessments called for in the protocol (**Sections 5.6 - 5.10**) study drug must be discontinued in instances where a major bleeding event

(defined in **Section 7.1**) is observed. Additional conditions where study drug must be discontinued are detailed in protocol **Section 2.7.1**.

7.6 Clinical Laboratory Evaluations

For this study, there will be both Local and Central laboratory blood draw requirements. The list below outlines which study specific laboratory blood draws are for central laboratory draws (using the provided central laboratory kit) and which are for local laboratory draws (using hospital stock supplies).

To avoid contamination or clotting, all coagulation tests taken for the purposes of this study should be obtained from an original arterial stick or venipuncture. If it is not possible to obtain blood from an original stick or venipuncture, blood may be collected from an arterial line in which no Heparin is infused. The arterial line will be flushed with NS both prior to and after the blood draw. No coagulation samples can be obtained from a Heparin infused or Heparin coated central line. Heparin must not be used when flushing an arterial line for this purpose. The site staff should use proper collection technique as described in the Central Laboratory Manual. **If an original arterial stick or venipuncture is then used to avoid clotting, the coagulation test tubes should not be the first tube of blood filled. Any other blood tests unable to be obtained from the original arterial stick or venipuncture may be taken from an existing port or line. If a central line is used, exploratory laboratory tests should be the last samples to be collected.**

7.6.1 Central Laboratory Tests:

The following laboratory assessments will be collected and sent to the central laboratory for analysis:

- Serum Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase and Total bilirubin)
- Arterial lactate concentration
- D-dimer
- Anti-drug Antibodies to ART-123
- Plasma thrombomodulin concentration (PK)
- Exploratory Laboratory Tests
    - Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII
    - Inflammation: CRP, Microparticles, and C5a

7.6.2 Local Laboratory Tests:

The following laboratory assessments will be collected for analysis at the local laboratory:

- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Serum Chemistry (Creatinine, Total bilirubin at Baseline Visit only; albumin and total bilirubin if not performed as SOC and necessary to calculate Child-Pugh in patients with severe liver disease at Screening)
- Pregnancy test; Serum or Urine human chorionic gonadotropin (hCG)
- Platelet count
- Coagulation Panel (Prothrombin time and INR)

7.6.3 Laboratory Sample Categories

There are four types of clinical laboratory evaluations: Safety, Coagulation Panel, Organ Dysfunction, and Exploratory.

Safety laboratory tests include the following:

- Serum Chemistry: Chemistry (Na, K, Cl, Bicarbonate, Glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase, Total bilirubin)
- Complete Blood Count with differential (RBC, Hemoglobin, Hematocrit, and WBC with differential count)
- Pregnancy test: Serum or Urine hCG
- Platelet count
- Antibodies to ART-123.

Note: All subjects that develop positive antibodies to ART-123 at Day 28 will be followed at 3 month intervals until their serum antibody titer level returns back to baseline or for a maximum of 18 months.

Coagulation Panel includes the following tests:

- Prothrombin time

- INR
- D-dimer

Organ Dysfunction labs include the following tests:

- Serum creatinine
- Total bilirubin
- PaO2/FiO2 ratio

Exploratory labs include the following tests:

- Coagulation: functional protein C, TAT, F1.2, PAI-1 and ATIII
- Inflammation: CRP, Microparticles, and C5a
- Plasma thrombomodulin concentration (PK)
- Arterial lactate concentration

7.7 Physical Examination

Physical examination is performed at the Baseline Visit. The physical will include general appearance; HEENT; neck; respiratory; cardiovascular; chest; abdomen; lymphatic; musculoskeletal and extremities; skin; and neurologic examination. Routine physical examinations will not be recorded after baseline. Any findings on the baseline physical, that are not attributable to a medical condition present prior to obtaining informed consent and meeting the last inclusion criteria, are to be captured either under a medical diagnosis on the Adverse Event eCRF or as a sign or symptom on the Adverse Event eCRF if not part of an diagnosis. All changes in physical examination from the time the subject met the last inclusion criteria and signed informed consent must be documented and recorded as an adverse event (either under a medical diagnosis or as a sign or symptom if not part of a diagnosis) in the eCRF.

7.7.1 Vital Signs

Vital signs include:

- Blood Pressure
- Respiratory rate
- Heart rate

- Temperature

7.8 Electrocardiogram (ECG)

A 12-lead ECG will be performed as outlined in the "Visit Schedule and Assessments" (beginning with **Section 5**) and the table outlining the "Schedule of Events" (**Section 5.19**). Subject's ECGs will be read centrally and the final read/interpretation of the ECG will be forwarded to the sites for filing in subject source records and documentation in subject's eCRF. Clinically significant changes in the ECG findings vs. baseline will be evaluated by the Principal Investigator and recorded as AEs / SAEs as applicable.

8 PROTOCOL AMENDMENTS

8.1 Protocol Amendments

Sponsor retains the responsibility for any protocol amendments. Any change or addition to this protocol requires a written protocol amendment that must be approved by the Regulatory Authorities and the IRB/IEC, as applicable, before implementation.

9 DATA MANAGEMENT

9.1 Documentation

Electronic Case Report Forms (eCRFs) will identify each subject by subject number (compilation of site number and subject number) and subject's initials (per local regulatory guidelines). Originals or copies of all source documents, and correspondence will be kept on file at the investigational site.

The data required by the protocol will be recorded in the appropriate eCRFs. All source data will be available to the study monitor who may perform a 100% data check (comparison of the data recorded in the eCRF with those in the source documents). The source data will also be available for an audit by the Sponsor or the FDA (Food and Drug Administration) and all applicable regulatory agencies at any time.

9.2 Data Collection

In addition to the eCRFs, individual subject files or subject medical records as well as Sponsor approved source data information will be maintained. Data will be entered into eCRFs. The eCRFs will be kept current, so that they reflect the latest observations on the subjects enrolled in the study. The eCRFs will include an audit trail to include changes made, reason for change, date of change, and person making changes.

The original signed informed consent form will be available for review at each study visit. All records will be kept in conformance to applicable national laws and regulations.

Analytical data from the central laboratory will be received in an electronic data file format for incorporation into the study database.

9.3 Database Management

When the subject specific database information has been declared to be complete and accurate the database will be locked. Any changes to the database after that time can only be made with written agreement of the Sponsor.

10 STATISTICAL CONSIDERATIONS

P-values will be reported as 2-sided p-values with the decision criteria discussed in **Section 10.1.1** evaluated using these values. Confidence intervals will be generally reported using traditional 95% two-sided intervals. The primary analysis for this study will be conducted on the data up through Day 28. Long-term survival status data will be analyzed once it becomes available following the analysis of the data through Day 28.

Randomization will utilize permuted blocks with a 1 to 1 ratio and will be stratified by site.

10.1 Sample Size and Power Considerations

The primary analysis for this study will be based on a stratified Cochran-Mantel-Haenszel test. For sample size and power calculations an unstratified Cochran-Mantel-Haenszel (chi-squared) test has been used. A sample size of 800 subjects provides 80% power if the following assumptions are made:

1. 5% two-sided α level

2. 8% treatment effect (24% placebo mortality rate vs. 16% ART-123 mortality rate)
3. 1 to 1 randomization

The assumed treatment effect and mortality rates are based upon post-hoc results from study 2-001 and assume the Day 28 mortality status will be known for all subjects.

If the true treatment effect is 12% (24% vs. 12%) a sample size of 800 provides greater than 80% power when a 0.1% alpha level is used.

These sample size and power calculations were performed with Pass 2007.

10.1.1 Decision Guidelines

The primary analysis of this Phase 3 trial is formally based on a two-category decision guideline. To be specific, the decision guideline for this trial is based on whether the observed two-sided p-value associated with comparison of the 28-day survival for the ART-123 arm vs. the placebo arm is, between 0.05 and 0.001 or less than 0.001.

1. If the two-sided p-value is between 5% and 0.1% then the ART-123-based regimen will have met the generally accepted level of evidence (false positive error rate) required to demonstrate efficacy.
2. If the two-sided p-value is less than 0.1% and supporting analyses corroborate this finding ART-123-based regimen will have provided highly reliable and statistically strong mortality results in a disease with limited treatment options. A second confirmatory study would then not be required.

In this 800 subject study an observed treatment benefit of approximately 6% is expected to result in a two-sided p-value less than 5% and a difference of approximately 9% is expected to result in a two-sided p-value less than 0.1%. A sample size of 800 subjects and these assumptions also provide 32% power for a 0.1% two-sided α level.

10.2 Analysis Populations

The primary efficacy analysis population will be the Full Analysis Set, FAS. The Full Analysis Set will consist of all randomized subjects who receive study drug and will be used for efficacy analyses. The Safety population will consist of all subjects who receive drug and will be used for safety analyses.

10.3 Study Stopping Rules / Interim Analyses

The Data Monitoring Committee (DMC) will use the following stopping rules regarding stopping the study early for safety, efficacy or futility.

10.3.1 Stopping for Safety

Termination or modification of the study due to safety concerns will not be limited to a fixed set of analyses. The DMC will be provided with unblinded safety data, including unblinded SAE reports, prior to scheduled data review meetings or upon request.

10.3.2 Stopping for Efficacy

Early termination of the study for efficacy will not be actively pursued unless it would be unethical to continue the study based upon the magnitude of benefit observed. In this situation should the primary efficacy results surpass an O'Brien-Fleming type boundary with Lan-DeMets implementation based upon a two-sided alpha level of 0.001 and the DMC believes the study results are extremely robust and so positive it is unethical to continue the study they may recommend termination for efficacy.

10.3.3 Stopping Due to Lack of Clinically Meaningful Benefit/Futility

An analysis to rule out clinically meaningful benefit will also be performed. The goal of these analyses is to stop the study if sufficient evidence exists that there is not a clinically meaningful treatment benefit. The futility analyses will be conducted with the use of a lower O'Brien-Fleming type boundary. This boundary will be constructed using a one-sided alpha level of 0.20 and the hypothesis: the 28-day mortality rate on ART-123 is reduced by 6%. Should interim analyses be performed after the 600 subjects time-point (75% information) the DMC will interpret the results of the futility calculations in context of the remaining enrollment.

10.4 Handling of Missing Data

Missing data will not be imputed for summarization; summary statistics will be reported based upon observed data.

Exception: for testing of the primary endpoint, Day 28 mortality status, subjects with unknown mortality status will be imputed. Investigators will be asked to assess if at the last point they had

contact with the subject, the subject's health was such that it was unlikely they would be alive at Day 28. If so, it will be assumed the subject was dead at Day 28 otherwise they will be classified as alive for the primary analysis.

10.5 Efficacy Analysis

10.5.1 Primary Analysis

The primary analysis will test the difference in the 28-day all-cause mortality rates between treatment groups in the Full Analysis Set. This analysis will be based upon a Cochran-Mantel-Haenszel test controlling for the randomization strata, site. Sites with low enrollment will be pooled. Subjects with missing mortality status at Day 28 will have their mortality status imputed as outlined in **Section 10.4**. To investigate the degree of variance reduction resulting from the stratification an unstratified test (chi-squared test) of the primary endpoint will be conducted.

Summary measures of survival status at the end of treatment and Day 14 will also be produced.

10.5.2 Secondary Analyses

Descriptive statistics will be used to summarize secondary endpoints. The difference in alive and event free days will be tested using a stratified Wilcoxon test (van Elteren test). Survival time will be summarized using Kaplan Meier methods and tested with a stratified log rank test.

10.6 Safety Analysis

10.6.1 Extent of Exposure

Duration of treatment and amount of drug received will be summarized.

10.6.2 Concomitant Medications

Concomitant medications will be coded by the World Health Organization (WHO) Drug Dictionary and tabulated by treatment group. Medication taken prior to treatment will be summarized separately.

10.6.3 Adverse Events

The incidence of adverse events (AEs), treatment-related AEs, AEs leading to discontinuation, serious adverse events (SAEs), fatal adverse events and AEs by severity will be tabulated by treatment received. These AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). For incidence reporting, if a subject reported more than one AE that was coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term. Once the patient is authorized to randomize, SAEs will be collected through Day 28. Once randomization has occurred both AEs and SAEs are collected.

10.6.4 Major Bleeding Events

The number of subjects with major bleeds, as defined in Appendix B, will be compared between treatment arms, as will the numbers of subjects with serious major bleeding events. The number of major bleeding events will be compared between groups at Days 3, 7, 14 and overall.

10.6.5 Clinical Laboratory Results

Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit. Subjects with clinical laboratory values outside of the normal reference range will be summarized.

10.6.6 Vital Signs and ECG

The observed data at baseline and change from baseline for each measurement day will be summarized with descriptive statistics.

11 PROCEDURES AND INSTRUCTIONS

11.1 Safety-Related Procedures

11.1.1 Reporting Responsibility

Serious adverse events will be reported immediately, not more than 24 hours after the investigative personnel first become aware of the event (see Appendix A for contact information).

The Investigator will report each SAE to the Sponsor within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported SAE

will also be reported to the Sponsor within 48 hours. The site is to follow their local regulations related to the reporting of SAEs to their local IRB/REB/IEC.

11.1.2 Reporting Procedures

The Investigator must complete the SAE report form in English, assess the relationship to study treatment, and send the completed form by fax or email to the Sponsor. Follow-up information should be submitted in the same manner as the original SAE form. The form and fax confirmation sheet or email will be retained in the site's investigator binder. Safety contact information has been provided in Appendix A of this protocol.

12 ADMINISTRATIVE PROCEDURES

12.1 Monitoring Procedures

During the study, the Sponsor or their designee will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to FDA regulations, ICH-GCP guidelines, and any local regulatory authority, the progress of enrollment, and also to ensure that study product is being stored, dispensed and accounted for according to specifications and applicable regulations. Key trial personnel will be available to assist the field monitor during these visits.

The Investigator will give the monitor access to all relevant clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will leave the study center. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

12.2 Recording of Data and Retention of Documents

The Investigator must complete the eCRFs and transmit the data, as instructed by the Sponsor and or designee. All entries to the eCRFs must be made as instructed by appropriate study personnel prior to each monitoring visit.

During the study, data collected on eCRFs about the subjects will be documented in an anonymous fashion and the subject will only be identified by the subject number and by his/her initials (per local regulatory guidelines). If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both the Sponsor and the Investigator are bound to keep this information confidential.

The Investigator must maintain any applicable source documents for each subject in the study, consisting of all demographic and medical information, and the signed informed consent form.

The Investigator will retain study related documents for as long as needed to comply with national and international regulations. The Sponsor will notify the Investigator(s)/institution(s) when the study-related records are no longer required.

12.3 Study Organization

12.3.1 Data Monitoring Committee

The Data Monitoring Committee (DMC) is responsible for the unblinded review of all Serious Adverse Events and overall safety data. The DMC will meet according to an agreed-upon schedule as detailed in the DMC Charter.

The DMC will consist of 3 members, one of whom shall be a biostatistician and the other two clinical experts. No DMC member may participate in the study. Unblinded reports to the DMC will be prepared by an unblinded independent statistician who will not participate in any study analysis.

Blinded presentations concerning study status will be made by Asahi Kasei Pharma America Corporation's medical representative or designee.

12.3.2 Publication of Results

Any formal presentation or publication of data from this study will require prior approval by the Sponsor, and may be considered as a joint publication by the Investigators and the Sponsor. Primary authorship may be determined by the Sponsor.

Publication of subsets of data will be subject to review by the Sponsor. All data remain the property of the Sponsor, except, of course, copies maintained at each site in compliance with ICH GCP and other regulations.

13 ETHICS AND GOOD CLINICAL PRACTICE

This study will be carried out in compliance with the protocol and in accordance with all applicable standard operating procedures (SOPs). These will be designed to ensure adherence to GCP, as described in:

ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.

Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

US 21 Code of Federal Regulations (CFR) (312) dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it, and thereby to adhere to the principles of GCP to which it conforms.

13.1 Institutional Review Board/Research Ethics Board/ Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects will be reviewed by a properly constituted IRB/REB/IEC. A signed and dated statement that the protocol and informed consent have been approved by the IRB/REB/IEC will be given to the Sponsor before study initiation. The name and occupation of the chairman and the members of the IRB/REB/IEC will be supplied to the Sponsor. This committee will approve any amendments to the protocol, other than administrative changes.

13.2 Informed Consent

Fully informed consent will be obtained before any study specific procedures are performed. The content and process of obtaining informed consent must be in accordance with all applicable ethical and regulatory requirements.

It is anticipated, by the very nature of the study that many subjects who will be eligible for this protocol will not be able to give fully informed consent themselves due to various reasons including sedation, unconscious state, etc. Therefore, in a situation where a subject is unable to provide consent for him/herself, informed consent will be obtained by using one of the following possible options, which must comply with an individual country's local laws and ethics committees regulating the enrollment of incapacitated adults into clinical trials.

This process must be expedited to ensure that securing an authorized representative's consent does not lead to delays that may result in increased risk to the subject. Furthermore, at no time will medical treatment be delayed to secure authorized informed consent for study participation.

Therefore, the following will be applied as long as your local laws allow:

- Consent from a LAR/AR / next of kin / legally appointed individual in person;

- Verbal consent from a LAR / AR / next of kin / legally appointed individual via telephone, confirmed by signed consent form sent by fax or email (at least 2 people from the study site are required, one to administer the informed consent and the second as a witness);
- Consent from a judge or specifically appointed lawyer for this purpose– if required by local regulations;
- In extreme and urgent circumstances when emergent action is required to mitigate the risk of death, it is understood that the presumed will of the subject will be determined by a physician and documented based on his/her knowledge of the study subject. As appropriate, an independent physician, who is a qualified medical doctor with at least one year's experience in intensive care medicine but must be from another department and/or hospital than the investigator, may sign the informed consent for the subject if the local laws, regulations and ethics committees approve this process. In countries where permissible, this independent physician may be from the same department. The study subject must be presented with the informed consent as soon as it is possible and reasonable, and informed consent obtained for continued study participation. The AR/LAR may act as an agent on the subject's behalf once they are available to provide informed consent.

When consent is obtained by fax via a LAR / AR / next of kin / authorized individual, an original signature must be obtained at the earliest opportunity.

Subjects enrolled in the study on the basis of consent by a LAR / AR / next of kin / legally appointed individual / independent physician will be given the opportunity to provide written confirmatory consent when and if they become able to do so. If the subject declines to confirm consent, they will be withdrawn from the study at the point where they decline consent.

In addition, where local regulatory and/or ethics committees allow, advance consent may be obtained prior to study entry in an attempt to obtain personal consent from the subject themselves.

Should a subject who is enrolled in the study on the basis of advance consent subsequently become unable to make medical decisions for him/herself, then the subject's legally acceptable next of kin / LAR should be informed of the subject's participation in the trial.

The above guidelines apply to all areas of the protocol where Informed Consent is referenced or required.

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15 APPENDICES

15.1 Appendix A: Serious Adverse Events

All Serious Adverse Events as defined in the Serious Adverse Event section of this protocol will be reported to the Safety and Pharmacovigilance Department using the contact information provided below. The logistical aspects will be defined in the study specific safety plan.

Fax: North America: 781-419-5028

Other Countries: Refer to study –specific regional fax number lists

Email: SAE@om.asahi-kasei.com

15.2 Appendix B: Key Study Definitions

Major Bleeding Events

A Major Bleeding event is defined as any intracranial hemorrhage, any life-threatening bleeding, any bleeding event classified as serious by the Investigator (e.g., resulting in permanent morbidity), or any bleeding that required the administration of at least 1440 mL (typically 6 units) of packed red cells over two consecutive days.[6]

All major bleeding events must be collected, documented, and promptly reported as SAEs.

Appropriateness of Initial Antibiotic Therapy

The Investigator will review all culture data from the time of infection onset to determine whether there is a definite identification of a causal organism (i.e., culture from a normally sterile site such as blood or pleural fluid), a likely identification of a causal organism (i.e., culture of suspected pathogen from another site with additional support [e.g., sputum culture where the sputum had < 10 epithelial cells and > 25 WBC per field]), or no causative organism identified. The Investigator will also review initial antibiotic therapy and organism MIC data, to determine whether it was appropriate for the known or suspected causative organism. Such review may include calculations of AUC/MIC relationships based on doses and anticipated clearances.

Mechanical Ventilation

Mechanical ventilation is described for the purposes of this protocol as any kind of ventilation administered via an endotracheal tube or nasotracheal intubation. This applies to all modes of ventilation (VA, VC and PC). Pressure Support Ventilation (PSV) is permissible. Simple administration of supplemental oxygen is NOT considered to be mechanical ventilation.

15.3 Appendix C: Definitions of Infection in the ICU

Clinical objective evidence of bacterial infection and being treated with antimicrobial medication(s):

The evidence of bacterial infection would include but not be limited to the following:

- Physical examination findings (i.e., cellulitis or abscesses)
- Positive culture(s) from normally sterile areas**
- Gram stain or other fluid/ tissue preparations (i.e., Direct Fluorescent Antibody, Nucleic Acid probes)
- Antigen detection in urine (i.e., *Legionella, Streptococcus pneumoniae*)
- Radiographic studies
- Surgical pathology specimens

** Note: A positive culture is not required

Infection is a pathological process caused by invasion of a host tissue or a normally sterile fluid or body cavity by pathogenic or potentially pathogenic bacteria that produce disease by multiplication, local tissue injury, and immune response/inhibition or toxin production.

Examples of compelling clinical objective evidence of bacterial infection (temperature and/or WBC may be required) include:

- Radiographic evidence of pneumonia associated with production of purulent sputum and a positive Gram stain or urinary antigen
- Radiographic evidence of perforated abdominal viscus (i.e., air under the diaphragm), except in cases of chemical peritonitis
- Presence of white blood cells in a normally sterile body fluid (e.g., cerebrospinal fluid or CSF)

Examples of cases lacking compelling clinical objective evidence of bacterial infection (temperature and WBC may be required):

- Bilateral basilar infiltrates without productive sputum and confirmation of bacterial infection with Gram stain, or urinary antigen
- Urine sample with some bacteria and no WBC
- Urine sample with a positive leukoesterase test or only a few WBC and no bacteria
- Abdominal tenderness accompanied by peritoneal signs in the absence of other objective evidence (ultrasound, CT, or surgical findings)

15.4 Appendix D: Organ Dysfunction Scale [22]

The following organ dysfunction/failure assessment is based on the ARDSnet organ dysfunction scale. The subject will be assessed, using this scale, daily from Baseline through Day 28. If the subject is discharged from the hospital, no further daily assessments are required after hospital discharge except on Day 14 and Day 28.

The presence of organ dysfunction will be determined based on laboratory or clinical parameters, as follows:

1. Hepatic: Any day with a bilirubin greater than or equal to 2.0 mg/dL will be counted as a hepatic insufficiency day, consistent with the ARDSnet criteria and a Sequential Organ Failure Assessment (SOFA) score greater than or equal to 2.[7,20]
2. Renal: Any day with a creatinine greater than or equal to 2.0 mg/dL is counted as a renal dysfunction day, consistent with the ARDSnet criteria and a SOFA score greater than or equal to 2.[7,18] Assess hemofiltration or dialysis use.
3. Respiratory: Any day that mechanical ventilation was used (except during surgery) is counted as a respiratory failure day. Assess PaO2/FiO2 ratio.
4. Shock (cardiocirculatory): Any day when a vasopressor is used will be counted as a shock day. Vasopressors include any use of norepinephrine, epinephrine, phenylephrine or vasopressin, or any use of dopamine at a dose greater than (>) 5 µg/kg/min. If vasopressin is used, it must be given in conjunction with another vasopressor.

15.5 Appendix E: Child-Pugh Scoring

Child-Pugh Score is a tool for classifying the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the INR and the degree of encephalopathy.

ASSESSMENT

Measure	**1 point**	**2 points**	**3 points**	**Units**
Bilirubin	< 2	2–3	> 3	mg/100mL
Serum albumin	> 3.5	2.8–3.5	< 2.8	g/100mL
INR	< 1.7	1.7–2.3	> 2.3	no unit
Ascites*	Absent	Slight	Moderate	no unit
Hepatic encephalopathy	None	Grade I–II	Grade III–IV	no unit

*As determined by physical examination alone

SCORING

Points	**Class**
5-6	A
7-9	B
10-15	C

15.6 Appendix F: West Haven Criteria for Grading of Mental Status in Hepatic Encephalopathy [21]

Grade	Criteria
I	Trivial lack of awareness Shortened attention span Impaired performance of addition Euphoria or anxiety
II	Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behavior Impaired performance of subtraction
III	Somnolence to semi stupor, responsive to verbal stimuli Confusion Gross disorientation, bizarre behavior
IV	Coma (unresponsive to verbal or noxious stimuli)

15.7 Appendix G: Prohibited Medications

The listing provided below includes medications that are most frequently given in the critical care setting. Please note that this list is not all-inclusive. There may be other medications that fall into a protocol prohibited medication class. The Sponsor should be contacted with any questions.

Antithrombotics* (thrombolytics, anticoagulants and antiplatelet drugs)

Vitamin K antagonists	Acenocoumarol • Clorindione • Coumatetralyl • Dicumarol (Dicoumarol) • Diphenadione • Ethyl biscoumacetate • Phenprocoumon • Phenindione • Tioclomarol • Warfarin
Heparin group	Danaparoid • Sulodexide
Glycoprotein IIb/IIIa inhibitors	Abciximab • Eptifibatide • Tirofiban
Other platelet aggregation inhibitors	Aloxiprin • Ditazole • Carbasalate calcium • Cloricromen • Dipyridamole • Indobufen • Picotamide • Ticagrelor • Triflusal • ADP receptor inhibitors (Clopidogrel, Ticlopidine, Prasugrel) • prostaglandin analogue (Beraprost, Prostacyclin, Iloprost, Treprostinil), Acetylsalicylic acid/Aspirin
Enzymes	Plasminogen activators (Alteplase/Reteplase/Tenecteplase, Streptokinase, Urokinase/Saruplase, Anistreplase) • other serine endopeptidases (Ancrod, Fibrinolysin) • Brinase
Direct thrombin inhibitors	Argatroban • Bivalirudin • Dabigatran • Desirudin • Hirudin • Lepirudin • Melagatran • Ximelagatran
Direct Factor Xa Inhibitors	Rivaroxaban • Apixaban • Edoxaban
Other antithrombotics	Defibrotide • Dermatan sulfate • Fondaparinux* • Otamixaban • Rivaroxaban
Non-medicinal	EDTA • Oxalate

*All of the above antithrombotics are excluded with the exception of:

a. Heparin locks/flushes

b. Prophylaxis for DVT per prophylactic dosing on the package insert as approved in your country. Examples include:

1. unfractionated heparin at total daily doses no higher than 15,000 U SQ
2. LMWH at a total daily dose no higher than 15000 U SQ
3. rivaroxaban 10 mg p.o. qd or 20 mg p.o. qd for prevention of recurrent DVT
4. enoxaparin 40 mg SQ qd
5. fondaparinux 2.5 mg SQ qd
6. danaparoid 750 units SQ q12h
7. desirudin 15 mg SQ q12h
8. apixabin 2.5 p.o. mg BID

c. Prophylaxis for cardiovascular disease:

1. Up to 325 mg of aspirin daily

d. Anticoagulants for RRT:

1. Regional citrate is preferred. It is recommended that if unfractionated heparin or LMWH is used, that the systemic exposure be less than or equal to the DVT prophylaxis dose allowed.

15.8 Appendix H: Chemotherapeutic Agents Known to Cause Myeloablation

The listing provided below includes medications that have a known side effect of myelosuppression. The Sponsor should be contacted with any questions.

Alkylating Agents	Busulfan • Bendamustine • Carboplatin • Carmustine • Chlorambucil • Cisplatin • Cyclophosphamide • Dacarbazine • Ifosfamide • Lomustine • Mechlorethamine • Melphalan • Oxaliplatin • Streptozocin • Temozolomide
Cytotoxic Agents	Azothiaprine • Bleomycin • Bortezomib • Busulfan • Capectabine • Carboplatin • Carmustine • Chlorambucil • Cisplatin • Cladribine, • Colaspase • Cyclophosphamide • Cytarabine • Dacarbazine • Dactinomycin • Daunorubicin • Docetaxel • Doxorubicin • Epirubicin • Etoposide • Fludarabine • Fluorouracil • Fotomusine • Ganciclovir
Anti-metabolites	Capecitabine • Hydroxyurea • Pemetrexed • Mercaptopurine • Methotrexate • Gemcitabine • Nelarabine • Clofarabine
Plant Alkaloids	Irinotecan • Topotecan • Etoposide • Paclitaxel
Topoisomerase Inhibitors	Hycamtin • Irinotecan • Novantrone

15.9 Appendix I: Toxicity/Adverse Event Grading Table

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

I. Instructions and Clarifications

Grading Adult and Pediatric AEs

The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

> Note: In the classification of adverse events, the term "severe" is not the same as "serious." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "serious" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the laboratory value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges

In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local laboratory LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1–3.8 mg/dL. A participant's actual laboratory value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

II. Definitions of terms used in the Table:

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISON OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (non-axillary)	37.7% – 38.6°C	38.7% – 39.3°C	39.4% – 40.5°C	> 40.5°C

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritus (itching – no skin lesions) (See also Injection Site Reactions: Pruritus associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	**≥** 180 mmHg systolic OR **≥** 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: in Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to ≥ 180 from > 180 (systolic) and to ≥ 110 from > 110 (diastolic).				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attention disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/attention disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 **–** 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% – 80%	FEV1 or peak flow 50% – 69%	FEV1 or peak flow 25% – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25% – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50% – 75% total surface	Epithelial disruption > 75% total surface

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25% - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50% - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			

DIVISON OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Comment: Parameter changed from “Infant, < 1 day” to “Infant, **≤**1 day”				

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18* – 6.79 *mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *> 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Comment: The decrease is a decrease from baseline				
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 - 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59- 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
Correction: Parameter changed from "Infant < 21 days" to "Infant ≤ 21 days"				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES ***Standard International Units are listed in italics***				
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences

DIVISON OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Comment: Some laboratories will report this value as bicarbonate (HCO_3) and others as Total Carbon Dioxide (bicarbonate). These are the same tests; values should be graded according to the ranges for bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatinine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Non-fasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Comment: Added ULN to Grade 1 parameter				
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 me/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 me/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 me/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 me/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 me/L *6.6 – 7.0 mmol/L*	> 7.0 me/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 me/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 me/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 me/L *2.0 – 2.4 mmol/L*	< 2.0 me/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 me/L *146 – 150 mmol/L*	151 – 154 me/L *151 – 154 mmol/L*	155 – 159 me/L *155 – 159 mmol/L*	≥ 160 me/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 me/L *130 – 135 mmol/L*	125 – 129 me/L *125 – 129 mmol/L*	121 – 124 me/L *121 – 124 mmol/L*	≤ 120 me/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS	**Standard International Units are listed in italics**			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

15.10 Appendix J: Conversions for PaO2/FiO2 calculations

Conversions for PaO2/FiO2 when the altitude is greater than 1000 m:

1) If your center uses Pb (Pb=barometric pressure in mmHg): Place the barometric pressure at your altitude into the equation PaO2/FiO2 x (Pb / 760 mm Hg)
2) If your center uses kPa: Place the atmospheric pressure at your altitude, into this equation PaO2/FiO2 x kPa/100 kPa.

O_2 Saturation Conversion Table[31] Pulse oximetry O_2 saturation may be used for Calculating PaO_2/FiO_2 ratio when ABG is not available	
SaO_2 (%)	**Calculated PaO_2**
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

Adapted from the equation developed by Severinghaus[31]: $SO2 = (23{,}400 * (pO_2^3 + 150 * pO_2)^{-1} + 1)^{-1}$

15.11 Appendix K: The APACHE II Severity of Disease Classification System[29]

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE — rectal (°C)	○ ≥41°	○ 39°-40.9°		○ 38.5°-38.9°	○ 36°-38.4°	○ 34°-35.9°	○ 32°-33.9°	○ 30°-31.9°	○ ≤29.9°
MEAN ARTERIAL PRESSURE — mm Hg	○ ≥160	○ 130-159	○ 110-129		○ 70-109		○ 50-69		○ ≤49
HEART RATE (ventricular response)	○ ≥180	○ 140-179	○ 110-139		○ 70-109		○ 55-69	○ 40-54	○ ≤39
RESPIRATORY RATE — (non-ventilated or ventilated)	○ ≥50	○ 35-49		○ 25-34	○ 12-24	○ 10-11	○ 6-9		○ ≤5
OXYGENATION: A-aDO_2 or PaO_2 (mm Hg) a. FiO_2 ≥ 0.5 record A-aDO_2	○ ≥500	○ 350-499	○ 200-349		○ <200				
b. FiO_2 < 0.5 record only PaO_2					○ PO_2 > 70	○ PO_2 61-70		○ PO_2 55-60	○ PO_2 < 55
ARTERIAL pH	○ ≥7.7	○ 7.6-7.69		○ 7.5-7.59	○ 7.33-7.49		○ 7.25-7.32	○ 7.15-7.24	○ <7.15
SERUM SODIUM (mMol/L)	○ ≥180	○ 160-179	○ 155-159	○ 150-154	○ 130-149		○ 120-129	○ 111-119	○ ≤110
SERUM POTASSIUM (mMol/L)	○ ≥7	○ 6-6.9		○ 5.5-5.9	○ 3.5-5.4	○ 3-3.4	○ 2.5-2.9		○ <2.5
SERUM CREATININE (mg/100 ml) (Double point score for **acute** renal failure)	○ ≥3.5	○ 2-3.4	○ 1.5-1.9		○ 0.6-1.4		○ <0.6		
HEMATOCRIT (%)	○ ≥60		○ 50-59.9	○ 46-49.9	○ 30-45.9		○ 20-29.9		○ <20
WHITE BLOOD COUNT (total/mm3) (in 1,000s)	○ ≥40		○ 20-39.9	○ 15-19.9	○ 3-14.9		○ 1-2.9		○ <1
GLASGOW COMA SCORE (GCS): Score = 15 minus actual GCS									
[A] Total ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variable points									
Serum HCO_3 (venous-mMol/L) [Not preferred, use if no ABGs]	○ ≥52	○ 41-51.9		○ 32-40.9	○ 22-31.9		○ 18-21.9	○ 15-17.9	○ <15

[B] AGE POINTS:
Assign points to age as follows:

AGE(yrs)	Points
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6

[C] CHRONIC HEALTH POINTS
If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:
a. for nonoperative or emergency postoperative patients — 5 points
or
b. for elective postoperative patients — 2 points

DEFINITIONS
Organ Insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria:

LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

CARDIOVASCULAR: New York Heart Association Class IV.

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respirator dependency.

RENAL: Receiving chronic dialysis.

IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

APACHE II SCORE
Sum of [A] + [B] + [C] :

[A] APS points _____

[B] Age points _____

[C] Chronic Health points _____

Total APACHE II _____

15.12 Appendix L: Glasgow Coma Scale[30]

Eye Opening		*Best Verbal Response*		*Best Motor Response*	
Spontaneous	4	Oriented	5	Obey commands	6
To Sound	3	Confused	4	Localize	5
To Pain	2	Inappropriate	3	Flexion: normal	4
Never	1	Incomprehensible	2	Flexion: abnormal	3
		None	1	Extension	2
				Nil	1

The scale consists of three separate responses: eye opening (E), verbal (V), and motor responses (M), each classified by a series of grades of responsiveness.