16.1.9 Documentation of Statistical Methods

This section contains the following document:

Statistical Analysis Plan (SAP) version 1.0 dated 18 Jun 2018

AsahiKASEI
ASAHI KASEI PHARMA AMERICA

Statistical Analysis Plan

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

Sponsored by:

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Date Approved: 18JUN2018

APPROVAL SHEET

Product:	ART-123
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1 Introduction

Sepsis has been defined as infection complicated by a systemic inflammatory response syndrome. Despite significant advances, 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.

Coagulopathy is associated with increased mortality in sepsis. Disseminated Intravascular Coagulation (DIC) has been well-described as an important risk factor for mortality in sepsis. Some data suggest that anticoagulation may improve survival in sepsis, while some clinical trials of sepsis therapies may have been confounded by concurrent anticoagulation. Irrespective of these findings, modulation of coagulation is a credible approach towards the realization of improved prognosis for subjects with sepsis and coagulopathy.

1.1 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 patient population.

Secondary:

- 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 Investigational Plan

2.1 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.

Following screening, subjects who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned, in a 1 to 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. The study period will be 28 days from the time of the start of treatment. Long term follow-up to determine mortality status will be conducted at 3, 6 and 12 months after the start of treatment.

The primary endpoint is all cause mortality status 28 days after the start of treatment (mortality day 28). Blood samples for assessing coagulation and inflammation parameters, ART-123 concentration, organ dysfunction, and safety laboratory tests will be obtained between baseline and the day 28 assessment. Safety-related assessments will include reports of adverse events, major bleeding events, ECGs and clinical laboratory test results.

The study will utilize an independent Data Monitoring Committee (DMC). The DMC's primary responsibility will be to review safety findings. There are also provisions for them to perform interim analyses for early stopping due to efficacy as well as futility.

The clinical database will be locked and analyses performed after the last subject has completed 28 days on study. At that time, the long-term mortality data will not be known for all subjects. These long-term mortality data will be collected and analyzed after the primary database lock and analyses.

2.2 Decision Guidelines

The primary analysis of this Phase 3 trial is formally based on a two-category decision guideline. Specifically, 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, the 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.

2.3 Sample Size

The primary analysis for this study will be based on a stratified Cochran-Mantel-Haenszel test. For sample size and power calculations a Chi-squared test has been used. A sample size of 800 subjects provides approximately 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).
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.

A sample size of 800 subjects and these assumptions also provides 32% power for a 0.1% two-sided α level. 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.

In this 800 subject study, an observed treatment benefit of approximately 6% is expected to result in a p-value less than 5% and a difference of approximately 9% is expected to result in a p-value less than 0.1%.

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

2.4 Method of Assigning Subjects to Treatment Groups

Randomization will utilize permuted blocks with a 1 to 1 ratio and will be stratified by site. Subjects will be randomly assigned to treatment at the baseline visit prior to dosing. For details concerning the time interval between meeting entry criteria, randomization and administration of study drug, refer to the protocol.

2.5 Blinding

Study drug is supplied as individual glass ampules containing blinded study drug (ART-123 or placebo). Study drug will be assigned and administered in a double blinded fashion, both the subject and the study site will be blinded as to the subject randomization.

In addition, Asahi Kasei Pharma America Corporation and the CRO's supporting the study will be blinded with the following exceptions:

1) The DMC will be unblinded. If the DMC believes it is imperative to unblind Asahi Kasei Pharma America Corporation the process and procedures outlined in the DMC charter will be followed.
2) The independent statistician supporting the DMC will be unblinded.
3) Designated personnel from the CRO supporting safety event reporting will be responsible for unblinding the safety events for regulatory reporting.

4) Although all site personnel are to be blinded, if it is medically imperative for the Investigator or authorized person to be unblinded they are to contact the Medical Monitor or designee to discuss the rationale for unblinding. The Investigator must document the rationale for and all activities associated with the unblinding and follow all procedures for reporting and recording of unblinding.

5) Drug supply and accountability services will be unblinded.

6) Central laboratory and exploratory laboratories, who handle pharmacokinetics data and biomarker data, will be unblinded.

7) Should a subject be ART-123 antibody positive the site will be required to follow the subject for antibody status. Not all subjects with a positive result on the assay will have taken ART-123. Designated personnel from the CRO supporting safety event reporting will be responsible for informing the sites of the need for additional follow-up.

Once the last subject has reached Day 28 and the appropriate data cleaning activities have taken place the clinical database through study day 28 will be locked and the sponsor will be unblinded. At this point follow-up to determine mortality status will continue. To limit potential bias study sites and study subjects will remain blinded to treatment assignment during this long-term follow-up.

3 STATISTICAL METHODS

3.1 Populations Analyzed

- Consented Population – All subjects who sign any informed consent. Subjects in the consented population will be analyzed based on the treatment group to which they were randomly assigned.
- Randomization Population – All subjects randomly assigned into a treatment arm.
- Full Analysis Set – The subset of the consented population who were randomly assigned to treatment and received at least one dose of study treatment. In this population subjects will be analyzed based upon the treatment group they were randomized to regardless of the study drug received.
- Safety Population – All subjects who received at least one dose of study treatment. In this population subjects will be analyzed based upon the study drug received. If subjects receive both ART-123 and placebo they will be included in the ART-123 group.

3.2 Study Endpoints

Primary Efficacy Endpoint:

- 28 day all-cause mortality

Secondary Efficacy Endpoints

- Follow-up all-cause mortality at 3 months
- Resolution of organ dysfunction through Day 28 (as defined in Section 5.15 of the protocol) as measured by
    - Shock free and alive days
    - Ventilator free and alive days
    - Dialysis free and alive days

Tertiary Efficacy Endpoints

- Follow-up 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 (as defined in Section 5.15 of the protocol).

Primary Safety Endpoints:

- Serious Adverse Events
- Major Bleeding Events
- Adverse Events

Secondary Safety Endpoint

- Anti-ART 123 antibodies

3.3 Study Day and Visit Windows

When study results are reported by time point (e.g., Day 3 or Day 28) the observation included at the time point will be based upon the actual date and time the event was recorded. Study Day and Study Hour, as defined below, as well as the Analysis Visit algorithm outlined in Table 1 will be used to determine how to map the observed results to time points. Analysis of Day 28 mortality and time till death will not use these conventions. These mortality analyses will be based upon days since the start of treatment and not these analysis visits as discussed in **Section 3.6.1** of this SAP.

Study Hour is calculated for any event for which time is recorded in the CRF. Study Hour is defined as,

Study Hour = Assessment Date and Time – First Dose Date and Start Time.

Study Hour is reported as XX.Y where XX is the hours between the events and Y is the decimal representation of the remainder minutes (e.g. 2 hours and 30 minutes is recorded as 2.5 and not 2.3). Study Hour may be negative for events that occur prior to treatment.

Study Day is defined as the days between the event and the start of treatment as follows:

Events that occur on or after 1st Dose:	Assessment Date – First Dose Date + 1
Events that occur before 1st Dose:	Assessment Date – First Dose Date.

Study Day as defined above and the study day defined in the protocol may not agree due to naming conventions and the fact that study day defined in the protocol is defined based upon hours from the start of treatment. For example, if the first dose occurs at 11:00 pm and vital signs are taken at 1:30 am the next day, the Study Day would be 2 for these vital signs and Study Hour would be 2.5. For reporting purposes, Study Day and Study Hour are used to assign the assessment to an Analysis Visit. In this example the vital signs would be reported on Analysis Visit = Day 1.

Analysis Visit, AVISIT, is defined based upon Study Hour (SH) when available and will occur between -24 and 164 hours. When Study Hour is unavailable or not within this range Analysis Visit is defined based upon Study Day (SD). See Table 1 below for the derivation of Analysis Visit.

Table 1 Analysis Visit

Analysis Visit	Analysis Visit Window	Nominal Time
-1	SH available and SH < -24 or SH not available and SD ≤ 0 and Event not recorded on the Baseline CRF Page	-24 hrs
0	SH available and -24 ≤ SH < 0 or SH unavailable and SD <= 1 and Event recorded on Baseline CRF page	0 hrs
1	0 ≤ SH < 20 or SH unavailable and SD = 1 and Event not recorded on the Baseline CRF Page	12 hrs
2	20 ≤ SH < 44 or SH unavailable and SD = 2	24 hrs
3 (3 pre, 3 post)	44 ≤ SH < 68: For the exploratory labs and PK results 3 pre or 3 post will be used depending upon if the sample collected was prior to or after the dosing or SH unavailable and SD = 3	48 hrs
4	68 ≤ SH < 92 SH unavailable and SD = 4	72 hrs
5	92 ≤ SH< 116 or SH unavailable and SD = 5	96 hrs
6	116 ≤ SH < 140 or SH unavailable and SD = 6	120 hrs
7	140 ≤ SH < 164 or SH unavailable and SD = 7	144 hrs
14	192 ≤ SH < 408 or 10 ≤ SD ≤ 18	14 days
28	552 ≤ SH < 744 or 24 ≤ Study Day ≤ 32.	28 days
24 Hours Post-Last Dose	Occurs in the window (12 hours post last dose, 36 hours post last dose). If more than one assessment falls within the window, the one closest in absolute hours to 24 hours post last dose will be chosen. If SH is unavailable Occurs in the window (Last Dose SD, Last Dose SD +1).	Null

SH = Study Hour, SD = Study Day

A record will be considered as the *analyzed record* provided it is the only record found within the analysis visit window. When multiple measurements for a particular parameter appear within a single window, the observation taken closer to the nominal time as defined in Table 1 will be considered the *analyzed record*. Hence, if a vital sign measurement is available at 23 and 30 hours past first dose, the 23 hours measurement is used for the data displays and summary statistics.

If multiple measurements are equidistant from the nominal time select the latter.

It is possible that a record may not be mapped to one of the above analysis visits due to the windowing structure. In this case, these records will be listed but not included in summary tables when presented by analysis visit.

3.4 Handling of Missing Data

For testing of the primary endpoint, Day 28 all-cause mortality status, subjects with unknown mortality status will be imputed. Investigators will be asked to assess whether 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 the subject will be classified as alive for the primary analysis. This imputation will only be used for the day 28 mortality status analysis.

3.5 Pooling Strategy for Strata

Testing for the primary and secondary endpoints will be stratified by site to reflect the randomization assignment. Stratification by site may result in observations being deleted from the analysis if there are no subjects in both treatment arms for an individual site. To ensure subjects are available for each treatment arm, individual sites having fewer than 8 subjects will be pooled together by region for testing purposes.

Regions include:

- North American,
- Western Europe (including Israel) + Australia + New Zealand, and
- Eastern Europe + the Rest of World.

Each region will have one pooled site.

3.6 Statistical Assessment of the Trial Objectives

3.6.1 Mortality Status

The primary hypothesis for this study is as follows:

$$H_o : M_{ART} \geq M_{plb}$$
$$H_a : M_{ART} < M_{plb}$$

Where in M_{ART} and M_{plb} are the mortality rates 28 days after treatment for the ART-123 and Placebo treatment arms. The primary analysis will test these hypotheses on the Full Analysis Set. The statistical test that will be used is a Cochran-Mantel-Haenszel test (LaVange, Durham and Koch, 2005) controlling for pooled site (see section 3.5). Subjects with missing/unknown mortality status at Day 28 will have their mortality status imputed as outlined in Section 3.4.

P-values will be reported as two sided p-values and compared to the two sided decision rules outlined in Section 2.2. Statistically significant positive results will be based upon achieving a reduction in mortality.

Mortality status 28 days after the start of treatment will be determined by evaluating the date of death if a subject died, or the last known contact date if the subject is not known to have died. If the date of death is 28 days or less from the start of treatment (Date of death – Date of first

treatment ≤ 28) the subject will be classified as dead at 28[1] after the start of treatment (Mortality Day 28). If the Date of death is more than 28 days after the start of treatment the subject is classified as alive at Mortality Day 28. Subjects without evidence of death will be classified as alive if their last contact date is 28 or more days after the start of treatment (Last Contact date – Date of first treatment ≥ 28). If the last contact date with a subject is less than 28 days after the first treatment the mortality status for the subject will be considered unknown and imputed as outlined in see Section 3.4.

Summary measurements of survival status will include the following:

a) Mortality status (dead, alive, unknown) at Study Day 3, 7 and 14
b) Kaplan Meier plots of time until death
c) Kaplan Meier estimate of mortality rates at Mortality Day 28

3.6.2 Long Term Mortality Status

Long term mortality status will be determined at 3, 6 and 12 months after start of treatment. This information will not be available for all subjects at the time of primary database lock. The analysis of long term mortality status will include Kaplan Meier based summarization of mortality rates at 3, 6 and 12 months as well as Kaplan Meier plots of time until death. Differences between treatment arms will be tested with a log rank test stratified by pooled site.

3.6.3 Day 28 Event Free and Alive Analysis

Event free and alive endpoints at the end of the study will be summarized with continuous variable descriptive statistics. Differences between treatment arms will be subjected to testing. These tests will look for a difference in the distribution of the number of event free and alive days between treatment arms. The test used will be a stratified Wilcoxon test (van Elteren test). The study has not been powered to test these differences and multiplicity adjustments for these tests will not be utilized. The 5 event free and alive endpoints include,

1. Shock free and alive days (secondary endpoint)
2. Ventilator free and alive days (secondary endpoint)
3. Dialysis free and alive days (secondary endpoint)
4. ICU free and alive days (tertiary endpoint)
5. Hospitalization free and alive days (tertiary endpoint)

The number of event free and alive days is defined as:

Alive Days –Event days

[1] The definition of Study Day can cause confusion concerning Day 28 mortality status. Twenty-eight days after the start of treatment is Study Day 29 and so Day 28 mortality status is determined by evaluating if a subject died on or before Study Day 29.

Alive Days

The number of alive days is the number of days a subject is alive during the first 28 days following the start of treatment. Specifically, this is calculated as,

i. Subjects who were alive on Study Day 29 will be assigned a value of 28
ii. Subjects who die prior to Study Day 29 will be assigned a value equal to:

Date of death – Date of first treatment

iii. Subjects with unknown mortality status at Study Day 29 will be assigned a value based upon the missing data imputation algorithm outlined in Section 3.4.
    a. Subjects classified as unlikely to be alive on Day 28 are given a value of

Date of last Contact – Date of first treatment + 1

    b. Otherwise the alive days is assigned a value of 28.

Event Days

The number of event days is the sum of days from Study Days 1 to 29 that an event was recorded. For more detail concerning this calculation see Section 4.3.2.

3.6.4 Organ Dysfunction and INR

The percent of subjects with Organ Dysfunction (Hepatic, Renal, Respiratory and Shock) and subjects INR scores will be summarized with descriptive statistics at Baseline, Day 3, Day 7, 24 hours post last dose, Day 14 and Day 28. For the organ dysfunction summary, the denominator will be subjects alive on the given mortality day (24 hours post last dose will not be summarized) and the numerator will be limited to subjects in the denominator. Subjects will be counted as having an organ dysfunction at each timepoint based on the analysis visit window structure found in Table 1of this SAP (if any of the events listed below occur within these windows the subjects is classified as having the dysfunction at that visit). Additionally, shift from baseline dysfunction status to post baseline status at each timepoint will be summarized. Organ dysfunction is defined as

Hepatic Dysfunction: Central lab bilirubin greater than or equal to 2.0 mg/dL

Renal Dysfunction: Central lab creatinine greater than or equal to 2.0 mg/dL

Respiratory Dysfunction: Mechanical ventilation as indicated from the ventilation log.

Shock Dysfunction: Vasopressor used as indicated on the vasopressor CRF page.

3.6.5 Sensitivity Analyses

The following sensitivity analyses will be performed on the primary endpoint.

- The difference between treatment groups with regards to time till death using all available information including follow-up will be assessed using a log rank test stratified by pooled site (Peduzzi, Henderson, Hartigan, and Lavori (2002)).

- The analysis specified for the primary endpoint will be done with no imputation for missing data.
- The analysis specified for the primary endpoint will be done assuming all subjects with unknown mortality status at day 28 are alive.

Additional sensitivity analyses which will be performed only for the interim analyses are detailed in section 3.8.

3.7 Safety Analyses

Safety endpoints will be summarized as outlined in Section 4.4. Testing will not be utilized. Confidence intervals will be produced for major bleeding events as discussed in section 4.4.6.

3.8 Interim Analysis

This study will include un-blinded interim analysis (IA) performed by a Data Monitoring Committee. There will be 4 IAs planned to occur when 150, 300, 450 and 600 subjects are evaluable for the 28 day all-cause mortality endpoint.

The DMC may recommend termination or modification of the study based upon a review of the totality of the data. Early termination of the study for efficacy will not be actively pursued however guidelines regarding this are provided in Section 5.

Analyses 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 will test the hypothesis given below:

$$H_o : M_{ART} < M_{plb} - 6\%$$
$$H_a : M_{ART} \geq M_{plb} - 6\%$$

Confidence intervals will be used to evaluate these hypotheses as outlined in Section 5.

Termination or modification of the study due to safety concerns will not be limited to a fixed set of analyses.

4 STATISTICAL SUMMARIES

4.1 General Conventions

Summary statistics will be presented by treatment group and overall.

Categorical data will be summarized and presented using counts and percentages for each treatment group. For categorical data, the percentage will be suppressed when the count is zero to highlight the non-zero results. The denominator for all percentages, unless otherwise specified, will be the number of subjects in each treatment group or overall within the analysis population.

For continuous variables, summary statistics will consist of the number of observations, mean, median, standard deviation, minimum, and maximum. All minimum and maximum values will be displayed with the same number of decimal places relative to the raw data, the mean and median will each have one additional decimal place, and the standard deviation will be displayed with two additional decimal places.

The trial period is divided into an active treatment period, defined as the dosing period followed by post-dose follow up, and a subsequent long-term follow up period see Section 5.2.1 of the Protocol, Table 1: Visit Schedule and Assessments.

All visits including unscheduled visits through 28 days will be re-mapped or derived according to the windowing algorithm in Table 1 and subject to rules laid out in Section 2.3. Presentation of summary measures will be by nominal time points corresponding to the remapped visits as seen in Table 1.

Any deviations from the originally planned analysis as specified in the Protocol will be detailed in the final clinical study report with an explanation of the alternative methods employed.

4.2 Study Population Summary

A table summarizing the number and percent of subjects by study population, Consented, Randomized, Safety, and Full Analysis Set will be provided by treatment group for all subjects screened. This summary will be broken down by treatment group for all subjects.

4.2.1 Subject Disposition

Subject disposition for FAS will be summarized through day 28 by randomized treatment group and overall. Two summary tables will be presented; one for study disposition and one for treatment disposition. The count and percent of subjects who completed the study through day 28 will be presented along with the reason for study discontinuation by treatment group and overall. Similarly, the treatment disposition table will include the count and percent of subjects which completed all six (6) study treatments and the reason for treatment discontinuation

A listing will present data concerning subject disposition on the FAS.

4.2.2 Protocol Deviations

4.2.2.1 Major Protocol Deviations

Major protocol deviations will be summarized. Major protocol deviations are

- Violations of an entry criteria.
- Incorrect treatment received.
- On treatment prohibited medication use as identified by a blinded sponsor review of medications
- Substantial overdose of study medication.

4.2.2.2 Violations of Inclusion/Exclusion Criteria

Two (2) summary tables will be presented. One will display the count and percent of subjects who met each inclusion criterion and the other will similarly display a summary for subjects which did not meet each exclusion criterion. On each of the respective tables a count and percent of subjects meeting all inclusion criteria (or did not meet any exclusion criteria) by treatment group and overall for each of the protocol versions.

Subjects violating any Inclusion and Exclusion Criteria, along with the actual violated criteria, will also be presented in a by subject listing for all consented subjects.

4.2.3 Demographics and Baseline Characteristics

Demographic data include age, age group (<65, ≥65), sex (Male, Female), race (American Indian / Alaska Native, Black / African American, Asian, Native Hawaiian / Other Pacific Islander, White, Mixed Race, Other), and ethnicity (Hispanic or Latino, Not Hispanic or Latino). Baseline characteristics include height, weight, baseline diabetes, baseline renal function (creatinine; <2 mg/dL, ≥2 mg/dL), baseline heparin use (any baseline medication with ATC of B01AB), arterial lactate (≤20 mg/dL, >20 mg/dL, and ≤55 mg/dL, >55 mg/dL), baseline renal replacement therapy (RRT), and APACHE II (Acute Physiology and Chronic Health Evaluation II) total score and the number and percentage of subjects with APACHE II total score < 25 and ≥25.

A blinded clinical review of medical history will be performed to identify subjects which are diabetic and this summary will be presented on the baseline characteristics table.

Demographics and baseline characteristics will be summarized for the FAS by treatment group and overall. All collected demographic and baseline characteristic data will also be presented on a by subject listing.

4.2.4 Summary of Septic Episode and Site of Infection

The number and percent of subjects will be summarized by treatment group and overall, in the FAS population, for the primary site of infection which includes heart, intra-abdominal, lung, and urinary tract. Primary sites of infection with fewer than 30 subjects will be pooled into an

"other" category and also summarized on this table. The number and percent of subjects with a culture sample taken, the result of those taken being either positive or negative, and the method will also be summarized on this table. The number and percent of subjects, on a separate table, with a culture taken will be summarized for the status of sensitivity to tested antibiotics. Additionally, a summary table of baseline antibiotic use will also be presented.

These data will also be presented in a by subject listing.

4.2.5 Medical History

A summary for medical history will be presented including the count and percent of subjects with a medical history record and also by body system and coded term. Furthermore, all data will be presented in a listing on the FAS.

4.2.6 Prohibited Concomitant Medications

A list of the prohibited concomitant medications for this study is found in Appendix G of the protocol. A summary table of prohibited concomitant medications will be presented for each treatment group and overall for using the FAS population. This table will include the count and percent of unique subjects having taken a prohibited medication while on study and also by drug class and preferred term. A by subject listing will also be presented.

4.2.7 Prior and Concomitant Treatments

4.2.7.1 Prior and Concomitant Medications

Prior and concomitant medications include the regular prior and concomitant medications and vasopressors Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary version WHODRUG enhanced version March 2014.

Prior and concomitant medications will be summarized separately and presented by drug class and preferred term at each treatment group and overall for the safety population. The count and percent of subjects with at least one of the respective medications (prior or concomitant) and also by drug class and preferred term will be presented as the summary. Subjects will be counted only once for each drug class and preferred term if they reported more than one medication within a given preferred term.

Concomitant medications will be any medication which was administered to the subject after first dose. Prior medications are those which are known to have ended prior to first dose. Medications that began prior to first dose and ended after first dose will be classified as both prior and concomitant medications.

Prior and concomitant medications will also be presented in listings by subjects in the safety population.

The imputation algorithm for partial and missing concomitant medication dates is provided in Appendix A.

4.2.7.2 Prior and Concomitant Surgeries and Interventions

Prior surgeries and interventions will be summarized by body system and coded term and will be also presented in a listing for the FAS. The count and percent of unique subjects will be presented by treatment group and overall for the FAS population.

Concomitant surgeries and interventions include ventilation, dialysis, and blood products. These will be summarized similarly as prior surgeries and interventions on a separate table in addition to all data collected, in the coded format, on the associated CRF page and also provided in their respective by subject data listings.

4.2.7.3 Vasopressor Use

A summary table displaying the number and percentage of subjects who received each type of vasopressor concomitant medication at baseline, Study Day 1, Day 7, Day 14 and Day 28, where the analysis time-points can be found in the visit window structure presented in Table 1 in this SAP, will be presented on the FAS population.

Vasopressor use will also be presented in a by subject listing.

4.2.8 Treatment Exposure

Dosing data will be summarized by treatment group for the Safety population using descriptive statistics to include duration of exposure (days). The count and percent of subjects who have total number of dose of 1, 2, 3, 4, 5 or 6 will also be presented.

Duration of exposure is calculated as: date/time of last dose – date/time of first dose, expressed in days with one decimal point.

Dosing information collected will also be presented in a by subject data listing.

4.3 Analysis of Efficacy Endpoints

4.3.1 Primary Efficacy Analysis

The primary analysis for the study will compare the 28-day all-cause mortality risk between the planned treatment groups in the FAS using a stratified Cochran-Mantel-Haenszel test controlling for the randomization strata site. Sites with low enrollment will be pooled. Pooling criteria has been described in section 3.5. Count and percent of subjects with known status (dead or alive) and also unknown status will be presented. Subjects with unknown mortality status at Mortality Day 28 will have their mortality status imputed as outlined in Section 3.4. For purposes of hypothesis testing, known dead and assumed dead subjects will be grouped together; similarly, known alive and assumed alive will also be grouped together.

4.3.1.1 Subgroup Analyses

Survival status at Mortality Day 28 will also be assessed on the following subgroups for the FAS population.

- Region, and Country
    - The difference between the two treatment groups will be presented as point estimate of the difference of 28 day survival rates and a 95% Wald Asymptotic confidence interval will be produced for region and country.
    - Region defined as;
        - North America: Canada, United States
        - Western Europe: Belgium, Finland, France, Germany, Greece, Israel, Netherlands, Spain, United Kingdom
        - Eastern Europe: Bulgaria, Croatia, Czech Republic, Hungary, Russia
        - Latin America: Argentina, Brazil, Colombia, and Peru
        - Pacific: Australia, New Zealand
        - Asia: Korea, Taiwan
        - India: India
- Sex
- Age group (<65, ≥65)
- Race
- Baseline diabetes (Y/N)
- APACHE II score category (score < 25 and ≥25)
- Site of infection
- Baseline Renal Replacement Therapy (RRT) (Y/N)
- Baseline renal function (<2mg/dL, ≥2mg/dL)
- Baseline heparin use (Y, N)
- Baseline arterial lactate (≤55 mg/dL, >55 mg/dL and ≤20 mg/dL, >20 mg/dL)
- Protocol Amendment version
- Violated any entry criteria (did or didn't violate any entry criteria)

The difference between treatment groups for these subgroups will be presented in summary tables and as forest plots with point estimates for the difference of mortality rates and associated Wald Asymptotic intervals. An asterisk (*) will be used to indicate on the summary tables any of the Wald confidence intervals which may be suspect due to a small sample size (i.e., fewer than 20 subjects in either treatment arm). Subgroup analyses will be presented for informative purposes only.

Additionally, a summary of survival status through mortality day 28 by new infections, concomitant Heparin use through day 7, renal function through day 7, and on-treatment Renal Replacement Therapy (RRT) (Y/N, RRT will be considered on-treatment provided it occurs within five days past last dose.) will also be presented similarly to the subgroup analysis above on the FAS population. These are post-baseline factors and may be correlated with treatment outcomes. No p-values will be calculated and the confidence intervals presented are for informative purposes only.

A table presenting count and percent of subjects who are known dead, known alive or have unknown status will be also presented for Study days 3, 7, 14, 28, 90, 180, and 360 as well as morality day 28 by treatment group and overall. The Kaplan-Meier survival estimates will be presented for each time-point although the survival estimate will not be presented for the total column. A stratified (by treatment) log rank test will be performed to assess the difference between treatment groups which will include all available mortality data as of the date of data cut, not just mortality data up to mortality day 28.

Kaplan-Meier plots of survival time will be also provided. Time to death is defined as the time from the first dose to death in days. Subjects without death records will be censored at the last point they were known to be alive.

Additionally, an investigation of the degree of variance reduction resulting from the stratification will be investigated with the use of an un-stratified test (Chi-squared test) of the primary endpoint.

4.3.2 Secondary Efficacy Analyses

4.3.2.1 All-cause Mortality at Month 3

The Kaplan-Meier method will be used to estimate the survival rate at month 3 (study day 87). Kaplan-Meier plots of survival time will be also provided. All long term follow up data at the time of analyses will be used to obtain month 3 Kaplan-Meier estimates. Subjects whose status is alive, or unknown will be censored at the last available date that the subject was known to be alive.

4.3.2.2 Shock, Ventilator, Dialysis Free and Alive days

Shock free, ventilator free, and dialysis free days will be analyzed using a stratified Wilcoxon test (Van Elteren test) with pooled site as the stratification factor. The number of event free and alive days is calculated as Alive Days – Event days. Alive Days are defined in Section 3.6.3. Each summary table will display a summary for number of Alive Days, Event free Days, and Event free and Alive Days. These tables will also be produced by baseline Renal Replacement Therapy status.

Shock days is defined as the number of days on concomitant vasopressor medication as collected in the eCRF vasopressor medication log.

Ventilator days are defined as the number of days on assisted breathing as collected in the eCRF ventilation log.

Dialysis days is defined as the number of days on dialysis as collected in the eCRF dialysis log.

4.3.2.3 ICU Free and Alive Days and Hospitalization Free and Alive Days

ICU free and alive days and Hospitalization free and alive days will be analyzed in a similar way as described in section 4.3.2.2.

ICU days is defined as the number of days staying in ICU as collected in the eCRF ICU log.

Hospitalization days are defined as the number of days spent in a hospital as collected in the eCRF Hospitalization log. If a subject is not discharged from the ICU or hospital within the 28-day period, the number of ICU/ Hospitalization free and alive days will be zero.

4.3.3 Additional Analyses

4.3.3.1 All - Cause Mortality for Month 6 and 12

All-cause mortality at month 6 (study day 177) and 12 (study day 350) will be analyzed in a similar way as that at month 3.

4.3.3.2 Organ Dysfunction

The organ dysfunctions of interest are hepatic, renal, respiratory, and shock dysfunction.

A summary table, using the FAS population, will be presented which will include the analysis time points, baseline, Study Day 3, Study Day 7, 24 hours post last dose, Study Day 14, and Day 28 as described in the analysis visit window structure in Section 3.3 of this SAP and the general definition for baseline. At each indicated time point, the number of subjects having survived to the nominal time point of the analysis visit will be presented. The denominator at each time point will be the number of subjects surviving to that particular time-point within each treatment arm or overall. The numerator will be the number of subjects with a particular organ dysfunction of interest at the time-point.

4.3.3.3 INR and Platelets

The INR values and change from baseline will be summarized with descriptive statistics at baseline, Study Day 3, 7, 24 hours post last dose, 14 and 28. Baseline will be defined as the last non-missing INR value prior to first dose. Furthermore, change from baseline calculations will only include subjects with non-missing values at both baseline and the specific post-baseline visit will be included. A summary of platelets will also be presented similarly.

4.3.3.4 Coagulation Panel, Organ Dysfunction and Exploratory Laboratory Results Analysis

Coagulation Panel includes the following tests:

- Prothrombin time
- INR
- D-dimer
- Platelet count

Organ Dysfunction labs include the following tests:

- Serum creatinine
- Total Bilirubin
- PaO2/FiO2 ratio (only if vented)

Exploratory labs include the following tests:

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

All efficacy laboratory evaluations will be presented in by-subject data listings.

Baseline is defined as the last non-missing value before first dose.

Summary statistics for actual values and for change from baseline will be tabulated for laboratory results by scheduled visit. Only subjects with baseline and non-missing post baseline values will be summarized at the specified time points. Figures of the mean (SD) and median (IQR) efficacy laboratory results (result and change from baseline) over time will be presented.

4.4 Analysis of Safety Endpoints

4.4.1 Clinical Adverse Events (AEs)

Adverse events will be categorized and presented by primary system organ class (SOC), preferred term (PT), and grade of severity. The preferred term will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The grade of severity will be estimated using the DAIDS Toxicity Table located in Appendix I of the protocol.

A treatment-emergent adverse event (TEAE) is defined as any AE following exposure to study treatment. For the purpose of calculating inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A. All AE tables will include the total number of events, counting multiple events per subject and the number and percent of unique subjects with at least one occurrence of a preferred term according to the most severe DAIDS grade. A listing of subjects who have experienced AEs, along with their respective AEs, is also provided.

The AE reporting period for this trial begins after informed consent is signed and final eligibility criteria met and ends on day 28. Safety evaluation will be performed based on the actual treatment a subject has received.

4.4.1.1 Incidence of Adverse Event

An overall summary of TEAEs will be provided to summarize of the following information: unique subjects experiencing any AE, subjects with TEAEs, subjects with any serious TEAEs, subjects with any AE resulting in death or, leading to permanent discontinuation of study drug, and any study drug related TEAE as well as unique subjects with any AE by maximum severity grade. These summaries will be done by treatment group and overall. Furthermore, the above summary table will be repeated for any AEs overall which will include all TEAEs.

TEAEs will be summarized by the number and percent of subjects in each primary SOC and preferred term. Subjects will be counted only once for each primary SOC and each preferred term.

All AE data will be presented in a by-subject listing.

4.4.1.2 Relationship of Adverse Events to Study Drug

A summary of TEAEs by relationship to study drug will be presented. A TEAE will be considered study drug-related if the investigator considered the event as possibly, probably or definitely related to treatment, or if the investigator assessment of the relationship is unknown. The TEAE data will be categorized and presented by primary SOC, preferred term, and relationship to study drug. Adverse events with missing relationship will be summarized as a related event and on the listings will be displayed as missing.

4.4.1.3 Severity of Adverse Event

A summary of TEAEs by primary SOC, preferred term, and severity will be presented in two tables. The first table will present mild/moderate TEAEs and the second table will present severe and potentially life threatening TEAEs. Subjects will be classified for each preferred term under the maximum severity experienced and summarized on the appropriate table. That is to say, if a subject experiences the same AE with a moderate and severe grade the subject will be counted on the second table and not the first.

4.4.1.4 Serious Adverse Events

Summary tables of serious AEs (SAEs) and related SAEs by primary SOC and preferred term by treatment arm will be provided. Furthermore, a summary of serious TEAEs leading to death will be presented.

All SAE data will be presented in a by-subject listing.

4.4.1.5 Premature Discontinuations Due to Adverse Events

Summary tables of AEs leading to study drug discontinuation by primary SOC and preferred term by treatment arm will be provided. Adverse events leading to study drug discontinuation will be listed by subject.

4.4.2 Clinical Laboratory Result Analysis

The safety labs include the following tests:

- Serum Chemistry: Na, K, Cl, bicarbonate, glucose, Ca, BUN, Creatinine, ALT, AST, Alkaline Phosphatase, total bilirubin (Central lab)
- Complete Blood Count with differential (Hemoglobin, Hematocrit, and WBC with differential count) (Local lab)
- Pregnancy test: Serum or Urine hCG (Local lab)
- Antibodies to ART-123 (Central lab)

If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summarization for >X and half the reported value used for <X.

Laboratory abnormalities will not be graded. All collected laboratory evaluations will be presented in by-subject data listings.

Baseline is defined as the last non-missing value before first dose.

Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by analysis visits as outlined in the analysis visit window structure found in section 3.3 of this SAP. Change from baseline calculations will only be summarized for subjects with non-missing baseline and post baseline values. Subjects with clinical laboratory values outside of the normal reference range will be summarized by shift tables. Figures of the mean safety laboratory result over time will also be presented.

The above summaries will be performed for the complete blood count with differentials, serum chemistry, and for hematology labs.

A listing of collected labs and their associated normal ranges will also be presented for both the global central lab and local lab data.

Additionally, an extreme range shift table for baseline to post-baseline value at post-baseline analysis visits as described in section 2.3 of the SAP will be presented by treatment arm on the safety population. The definition of extreme ranges for specified labs is given in appendix B of this SAP.

4.4.3 Antibody Analysis (Anti-drug antibody to ART-123)

Anti-drug antibodies to ART-123 will be evaluated and presented in a listing. A summary of antibody analysis results will be presented by treatment group, overall, and for each visit. This summary table will include the number of screening assays analyzed and the number and percent of subjects having positive and negative results from the analyzed assay including the screening and confirmatory assay. All collected antibody data will be presented in a by subject listing. Titer and Neutralizing antibody results will only be available for subjects with confirmed positive ADA results.

4.4.4 ECG

Subject's ECGs will be read centrally and the final read/interpretation of the ECG will be forwarded to the sites. ECG results, including general findings, heart rate (beats/minute), and PR, QRS, and QTc intervals (seconds) will be available. A change from baseline summary table will be presented. Also, a shift from baseline table by normal/abnormal flag, as defined Table 2 will be presented for all scheduled post dose visits and will display the number and percent of subjects for each shift.

Table 2: ECG Normal Range

Interval	Normal	Abnormal, Clinically Insignificant	Abnormal, Potentially Clinically Significant
HR	50-100 bpm	40 - < 50 or > 100 – 150 bpm	< 40 or > 150 bpm
PR	120 – 220 msec	< 120 or > 220 – 240 msec	> 240 msec
QRS	≤ 110 msec	111 - 120 msec	> 120 msec
QTcB (QTcF)	Female: ≤ 470 msec Male: ≤ 450 msec	Female: > 471 - 500 msec Male: >451 - 500 msec	Female: > 500 msec Male: > 500 msec

The observed data at baseline and change from baseline for each scheduled post dose visits will be summarized with descriptive statistics. Change from baseline will only be calculated for subject having non-missing baseline and post baseline measurements. The number of subjects with a QTc result > 500 msec or a change from baseline > 30 msec or > 60 msec will be summarized at each visit. A by-subject listing of ECG recordings will also be provided. All summaries presented will be by actual treatment group.

ECG data will be presented in a by subject listing.

4.4.5 Vital Sign Measurements

The vital sign measurement panel will include blood pressure, respiratory rate, heart rate, and temperature. Observed results at each visit will be presented. The vital sign data at baseline and change from baseline for each scheduled post dose visit will be summarized with descriptive statistics by actual treatment group. Change from baseline will only be calculated for subjects having non-missing baseline and post-baseline measurements.

All vital sign measurements will be presented in a by subject listing.

4.4.6 Bleeding Events

A summary table for the number and percent of unique subjects with at least one major bleeding event during the 28 day study period, along with 95% exact confidence interval of the bleeding rate for each treatment and the exact risk difference between two treatment groups in bleeding rates, will be presented using the safety population. The count and percent of unique subjects experiencing at least one bleeding event by Study Days 3, 7, and 14 will be presented in the same table, but confidence intervals and risk difference will not be provided. Subjects will be counted as having experienced a major bleeding event from the earliest recorded event through all subsequent time points.

A bleeding event is considered on-treatment provided it occurs within five days past last dose. An after-treatment event is any event with an onset date of six or more days past last dose date. A summary of on-treatment and after-treatment major bleeding events will be presented by treatment arm and overall. If a subject experiences both an on-treatment and after-treatment event the subject will be counted in both summaries; that is, on-treatment and after-treatment event summaries may not be disjointed.

A similar summary will be presented for serious major bleeding events as well.

Additionally, the differences in major bleeding event rates will be presented by country, new infections, concomitant heparin use through day 7, renal function through day 7, baseline RRT, and on treatment RRT

Adverse events and serious adverse events identified as bleeding events will be summarized by primary system organ class (SOC) and preferred term (PT) for on treatment and off treatment separately.

All bleeding event data will be presented in a data listing.

4.4.7 Pregnancies

A by-subject listing will present pregnancy results, including serum or urine hCG, for subjects who are pregnant based in the FAS population.

4.5 Pharmacokinetic Analyses

Plasma concentration data will be summarized in tables and figures by actual treatment group by sampling timepoints (pre and post dose sampled displayed separately) as outlined in Table 1. The results will also be presented in a listing.

Plasma concentration data will also be presented by treatment group in a by subject listing.

5 Interim Analysis

Only subjects randomized prior to the DMC database lock date (i.e., 8 weeks prior to the DMC meeting) will be considered evaluable for the primary efficacy and futility analyses at each of the interim analyses.

Early termination of the study for efficacy will not be actively pursued. However, should the primary efficacy results surpass an O'Brien-Fleming type boundary using 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 of the study for efficacy. The alpha level for this O'Brien-Fleming boundary has been selected to result in a negligible impact on both decision rules outlined in Section 2.2 The impact on the final alpha level at the 0.1% level is very small but is non-zero. The alpha spent at the interim analysis is approximately 0.00005. Due to the small size of this alpha spend no adjustment to final alpha level will be made.

Early termination for futility will be assessed using a Mantel-Haenszel difference of proportions with pooled site as a stratification factor. If the lower bound of the confidence interval around the difference of proportions (M_{ART} - M_{Plb}) exceeds -0.06 then this will be considered sufficient evidence to rule out clinically meaningful benefit. The alpha spending rule and corresponding confidence interval that will be produced for each DMC plus the final analysis will use a Lan-DeMets approach. The Table 3 is an example of how the alpha spending would look if the interims occurred at 150, 300, 450 and 600 subjects as planned.

Table 3 Alpha Spending for Interim Analyses

Interim #	CI %	Nominal α	Cumulative α
1	99.7%	0.003	0.003
2	96.5%	0.035	0.036
3	92.3%	0.077	0.087
4	88.8%	0.112	0.139
Final Analysis	84.5%	0.155	0.200

The effect of this futility analysis on the overall power of the study is small, but non-zero. There is a 0.6% chance of stopping the study for futility if the actual difference in 28 day mortality is 8% in favor of treatment (16% vs. 24%).

Interim analysis outputs will be programmed initially using dummy treatment codes by a blinded biostatistics team. The programs will be sent to the unblinded statistician supporting the DMC and rerun using the actual unblinded treatment codes. All interim analysis outputs will be based upon the randomized treatment assignments.

6 References

Lan, K., and DeMets, D., (1989). Changing frequency of interim analysis in sequential monitoring. *Biometrics* Vol. 45, 1017-1020.

LaVange, L., Durham, T., and Koch, G., (2005). Randomization-based nonparametric methods for the analysis of multicentre trials. *Statistical Methods in Medical Research* Vol. 14, 281-301.

O'Brien, P., and Fleming T. (1979). A multiple testing procedure for clinical trials. *Biometrics* Vol. 35, 549-556.

Peduzzi, P., Henderson, W., Hartigan, P., and Lavori, P. (2002). Analysis of randomized controlled trials. *Epidemiologic Reviews*, Vol. 24, No. 1, 26-38.

7 APPENDIX

7.1 Appendix A

Adverse Events

If onset date is completely missing, onset date is set to date of first dose.
If (year is present and month and day are missing) or (year and day are present and month is missing):

If year = year of first dose, then set month and data to month and day of first dose
If year < year of first dose, then set month and day to December 31.
If year > year of first dose, then set month and day to January 1.

If month and year are present and day is missing:

If year = year of first dose and
If month = month of first dose then set day to day of first dose
If month < month of first dose then set day to last day of month
If month > month of first dose then set day to first day of month
If year < year of first dose then set day to last day of month
If year > year of first dose then set day to first day of month

For all other cases, set onset date to date of first dose.

Prior and Concomitant Medications

Impute partial/missing start date with earliest possible date, and end date with latest possible date.
If start date of medication is completely missing in which the day, month, and year are all unknown or only the day is known, then the start date will not be imputed.

For the partial start date of medication,

- If the year is present and the month and day are missing or the year and day are missing, set month and day to January 1
- If the year and month are present and the day is missing, set day to 1st day of month.
- If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.
-

If the end date of medication is completely missing, in which the day, month, and year are all unknown or only the day is known, then the end date will not be imputed.

For the partial end date of medication,

- If the year is present and the month and day are missing or the year and day are present and the month is missing, set month and day to December 31.
- If the year and month are present and the day is missing, set day to last day of the month.

Medications with both missing start and end date after imputation will be considered as both prior and concomitant medications.

7.2 Appendix B

Table 4 Extreme Low and High Values for clinical labs

Ranges	Unit	Values outside this range are considered extreme
Blood count		
Hemoglobin	g/dl	6 – 18.3
Hematocrit	%	18 – 55
White blood cells	10^3/µL	3 - 30
Neutrophils	%	40 – 97
Eosinophils	%	none – 5
Basophils	%	none – 3
Lymphocytes	%	3 – 40
Monocytes	%	none – 9
Bands	%	none – 25
Blasts	%	none – 3
Atypical Lymphocytes	%	none – 10
Platelets	10^3/µL	30 – 800
Blood Chemistry		
Sodium	meq/L	120 -155
Potassium	meq/L	2.2 – 6.5
Chloride	meq/L	85 - 120
Bicarbonate	meq/L	10 – 45
Glucose	mg/dL	40 - 400
Calcium	mg/dL	6 – 13
Urea/Bun	mg/dL	2 – 100
Creatinine	mg/dL	0.2 – 10
ALT	U / L	1-800
AST	U / L	1-800
Alkaline Phosphatase	U / L	10-800
Lactate Dehydrogenase	U / L	5 – 1500
Total bilirubin	mg/dL	0.1 - 5.0
INR	ng / ml	0.5 – 4
D-Dimer		500 – 10,000
Fibrinogen	mg / dl	100 - 800