Acetaminophen in Sepsis: Targeted Therapy to Enhance Recovery (ASTER)

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Summary of revisions:

- Pg 4: Section 1.4.2 Sample Size/Statistical Considerations: Sentence added: *Using clinical trial data from the PETAL Network, the estimated standard deviation of 28-day organ support free days (obtained from the PETAL Network CLOVERS study) is 8.7 days.*
- Pg 10: Section 2.6 Interim Analysis: References added to the second paragraph:

  1] Martin, G.S., et al., The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med, 2003. 348: p. 1546-1554.
  [2] Haybittle, J.L., Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol, 1971. 44(526): p. 793-7.

- Pgs 12 and 13: Safety Outcomes section: References noted in paragraphs 3 and 5 footnoted and placed in Reference section.

- Page numbering added to document and formatting edits made.

Revisions reviewed and approved by PETAL CCC PI Andrea Foulkes

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Contents

1.Trial Summary

1.1 Title

Acetaminophen and Ascorbate in Sepsis: Targeted Therapy to Enhance Recovery (ASTER)
ASTER is a platform originally designed to conduct two separate trials. In response to external trial results, enrollment in the Vitamin C arm of the trial was suspended on June 15, 2022. The Acetaminophen (APAP) arm of the trial was resized and will continue as described in this amended protocol.

1.2 Objective

Objective: To carry out one multi-center phase 2b randomized double-blinded placebo-controlled trial of one pharmacologic therapy. The trial will assess the efficacy of Acetaminophen (1 gram intravenously every 6 hours) in comparison to placebo for 120 hours in patients with sepsis who have evidence of either hemodynamic or respiratory organ failure. The placebo infusion (5% dextrose in water, D5W) will match the volume and storage temperatures of the acetaminophen (room temperature, dose adjusted for weight below 50 kg)

1.3 Hypothesis

Hypothesis: Acetaminophen (APAP) infusion will increase the days alive and free of organ support to day 28.

1.4 Study Design

Prospective multi-center phase 2b randomized placebo-controlled double-blinded interventional trial of intravenous Acetaminophen for patients with sepsis-induced hypotension or respiratory failure.

1. Enrollment Period: Approximately 15 months
2. Patient Population: Critically ill adults admitted or planned admission to the ICU with sepsis and either hemodynamic or respiratory organ failure. A maximum of 450 patients will be enrolled
3. Locations: Emergency Department and ICUs at hospitals participating in the NHLBI PETAL Network

1.4.1 Treatment Arms

Patients with sepsis and either hemodynamic or respiratory organ failure on enrollment will be randomized to one of two treatment arms in a 1:1 fashion. The two arms will be Acetaminophen and Placebo randomized 1:1.

1. Acetaminophen given intravenously at the dose of 1 gram (or 15 mg/kg if patient weighs < 50 kg) every six hours for 5 days (20 doses) ***OR***

2. Placebo (identical appearing 5% dextrose solution) infused every six hours for 5 days (20 doses)

NOTE: The volume of placebo infusions will be lower in patients <50kg and will be matched to Acetaminophen.

Patients, nurses, research staff, and physicians will be blinded to the treatment assignment. The time of randomization will represent time zero. Study drug will be started within 4 hours of randomization**.**

Duration	Timing of Dosing	Subsequent Dosing
Treatment will continue for **120 hours (20 doses**), or discharge from the intensive care unit, study withdrawal, or death, whichever comes first.	*First study drug dose* (APAP or placebo) will be considered "Dose 1" and will be administered within **4 hours of randomization**. Study drug will be infused over 30 minutes.	**Subsequent doses will be infused every six hours (+/- 1 hour) through 120 hours or 20 doses (whichever comes first).** If a dose cannot be administered within 3 hours of the scheduled time, the dose should be skipped. Any dose administered outside of the +/- 1 hour window or any dose that is skipped will trigger a protocol deviation

2. **Completion of study drug administration**: Study drug administration will occur for a total of 120 hours, unless one of the following occurs:
    1. Discharged from the study hospital
    2. Discharge from the ICU
    3. Withdrawal from the study
    4. Death
    5. New AST or ALT elevation ≥ 10 times the upper limit of normal

1.4.2 Sample Size/Statistical Considerations:

Using clinical trial data from the PETAL Network, the estimated standard deviation of 28-day organ support free days (obtained from the PETAL Network CLOVERS study) is 8.7 days. With randomization of 450 total patients (225 Acetaminophen 225 placebo) we will have 85% power to detect a difference between groups of 2.5 days in the primary composite outcome of days

alive and free of organ support (dialysis, assisted ventilation, and vasopressors) to day 28. Patients will be analyzed on an intention-to-treat basis based on randomization assignment.

1.5 Inclusion Criteria

1. Age ≥ 18 years
2. Sepsis defined as:
   a. Clinical evidence of a known or suspected infection and orders written to administer antibiotics

   AND

   b. Hypotension as defined by the need for any vasopressor (and at least 1 liter of fluid already administered intravenously for resuscitation) **OR** respiratory failure defined by mechanical ventilation, BIPAP or CPAP at any level, or greater than or equal to 6 liters/minute of supplemental oxygen (criterion b must be present at the time of randomization)
3. Admitted (or intent to admit) to a study site ICU within 36 hours of presentation to the ED or any acute care hospital

1.6 Exclusion Criteria

1. No consent/inability to obtain consent from the participant or a legally authorized representative
2. Patient unable to be randomized within 36 hours of presentation to the ED or within 36 hours of presentation to any acute care hospital
3. Diagnosis of cirrhosis by medical chart review
4. Liver transplant recipient
5. AST or ALT greater than five times the upper limit of normal
6. Diagnosis of ongoing chronic alcohol use disorder/abuse by chart review; if medical record unclear, use Appendix F
7. Hypersensitivity to Acetaminophen
8. Patient, surrogate or physician not committed to full support (Exception: a patient will not be excluded if he/she would receive all supportive care except for attempts at resuscitation from cardiac arrest)
9. Home assisted ventilation (via tracheotomy or noninvasive) except for CPAP/BIPAP used only for sleep-disordered breathing
10. Chronic dialysis
11. Use of home oxygen > *3 liters/min nasal cannula* for chronic cardiopulmonary disease
12. Moribund patient not expected to survive 24 hours
13. Underlying malignancy or other condition with estimated life expectancy of less than 1 month

14. Pregnant woman, woman of childbearing potential without a documented negative urine or serum pregnancy test during the current hospitalization, or woman who is breast feeding
15. Prisoner
16. Treating team unwilling to enroll because of intended use of Acetaminophen

1.7 Primary Endpoint

Primary efficacy variables will be evaluated comparing Acetaminophen vs. placebo The primary efficacy variable is days alive and free of organ support (dialysis, assisted ventilation, and vasopressors) to day 28.

Participants will need to be free of all three components (assisted ventilation, vasopressors, new renal replacement therapy) to qualify for a day alive and free from organ failures. A patient could be free of all organ failures from day 10 through day 22 and then die on day 22 and would receive 12 days of credit for this primary outcome. The components of this outcome (days free of dialysis, assisted ventilation, and vasopressors in the overall cohort and in survivors, and 28-day all-cause all-location mortality will also be reported as secondary outcomes (see below in 2.1).

1.8 Secondary Endpoints

Secondary efficacy variables will be evaluated comparing Acetaminophen vs. placebo.

1. 28-day ventilator-free days
2. 28-day vasopressor-free days
3. 28-day new renal replacement-free days
4. 28-day hospital mortality
5. 28-day ICU free-days
6. 28-day hospital-free days to discharge home
7. 28-day duration of ICU stay in survivors and non-survivors
8. Initiation of assisted ventilation to day 28
9. Initiation of renal replacement therapy to day 28
10. Change in Sequential Organ Failure Assessment (SOFA) scores between enrollment and study day 7
11. 90-day hospital mortality (includes death at any healthcare facility that is not the equivalent of home for a patient)
12. Development of ARDS within 7 days of randomization
13. Change in serum creatinine from enrollment to discharge, death, initiation of dialysis or 28 days, whichever occurs first
14. Major Adverse Kidney Events at 28 days (MAKE28): persistent increase in serum creatinine by 200% from baseline, need for new renal replacement therapy, or death

15. Change in the Radiographic Assessment of Lung Edema (RALE) score from enrollment to study day 3 in patients who are receiving assisted ventilation or high flow nasal oxygen at baseline.
16. 90-day all-cause mortality

1.9 Safety Variables

The safety monitoring and analyses will be performed separately on the Acetaminophen and placebo arms (1 active to 1 placebo randomization ratio). The safety variables will include the following:

1. Hypersensitivity or rash
2. AST and ALT measured on study days 0, 2-5, and 7 (day 7 measurement can be ±1 day) in the APAP-Active/APAP-Placebo arm only.
3. The plasma levels of Acetaminophen will be obtained as a trough level just prior to administration of a study dose on study day 2 (subject must have received at least 5 doses of study drug before the day 2 samples are obtained) for all patients. After the first 100 patients have been enrolled who have been randomized to the Acetaminophen arm, the trough levels will be reported to the DSMB to determine if they exceed the level of 20 micrograms/mL, the potential level for hepatotoxicity.
4. Administration of fluid bolus, new use of vasopressor, or increased dose of vasopressor within 120 minutes of study drug infusion.
5. Incidence of reported adverse events

2. Endpoints

2.1 Primary Outcome

The primary endpoint of this trial is to evaluate the effects of intravenous Acetaminophen compared to placebo on the number of days alive and free of assisted ventilation, vasopressors and new renal replacement therapy between the treatment arm and the placebo group over the first 28 days.

Note that the primary outcome components to be reported will be:

1. 28-day all-location all-cause mortality
2. Days free of assisted ventilation to day 28 in the overall cohort and survivors
3. Days free of new RRT to day 28 in the overall cohort and survivors
4. Days free of vasopressors to day 28 in in the overall cohort and survivors

The primary safety objective is to determine the effect of intravenous Acetaminophen on markers of liver injury (AST and ALT) measured on days 2-5, and 7 (day 7 measurement can be ±1 day).

2.2 Secondary Outcomes

We will compare the efficacy of intravenous Acetaminophen to placebo for efficacy endpoints.
We will compare the safety of Acetaminophen to placebo for safety endpoints.

1. **28-day ventilator-free days:** VFDs depend on both duration of ventilation and mortality through study day 28. In participants who survive 28 days, VFD is defined as 28 minus days of invasive or noninvasive ventilation to day 28. Duration of ventilation is counted from the first study day of assisted breathing through the last day of assisted breathing provided the last day is prior to day 28. For participants discharged with assisted ventilation (e.g., to LTAC facility) prior to day 28, a phone call will be required to assess ventilator and vital status at day 28. Participants discharged prior to day 28 on unassisted breathing will be assumed to remain on unassisted breathing through day 28. Isolated periods of ventilation briefer than 24 hours for surgical procedures and ventilation solely for sleep disordered breathing do not count towards duration of ventilation. In participants who never require assisted breathing, duration of ventilation is zero. Participants who do not survive 28 days will be assigned zero VFD.
2. **28-day vasopressor-free days:** Vasopressor free days to day 28 are defined as the number of calendar days between randomization and 28 days later that the patient is alive and without the use of vasopressor therapy. Patients who die prior to day 28 and those who receive vasopressor therapy for the entire first 28 days are assigned zero vasopressor free days.
3. **28-day new renal replacement-free days:** Renal replacement free days to day 28 are defined as the number of calendar days between randomization and 28 days later that the patient is alive and without renal replacement therapy. We also follow the "last off" method. Patients who died prior to day 28 and those who receive renal replacement therapy for the entire first 28 days are assigned zero renal replacement free days.
4. **28-day hospital mortality**
5. **28-day ICU free days:** ICU free days to day 28 are defined as the number of days spent alive and out of the ICU to day 28.
6. **28-day hospital free days to discharge home:** Hospital free days to day 28 are defined as 28 days minus the number of days from randomization to discharge home. If a patient has not been discharged home prior to study day 28 or dies prior to day 28, hospital free days will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.
7. **Duration of ICU stay in survivors and non-survivors**: The total number of days spent in the ICU until hospital discharge or death during the first 28 days. If a patient is discharged alive from the study hospital we assume they are no longer in the ICU.
8. **Initiation of assisted ventilation to day 28**: Any patient who received assisted ventilation in the first 28 days meets this endpoint. If a patient leaves the hospital without initiation of assisted ventilation, we assume they never started.
9. Initiation of new renal replacement therapy to day 28.
    - Patients who receive (new) renal replacement therapy through day 28 will meet this endpoint.
10. **Change in organ-specific Sepsis-related Organ Failure Assessment (SOFA) scores between enrollment and day 7:** We will calculate the SOFA score upon

enrollment and at day 7 using clinically available data. If a value is not available at baseline, it will be assumed to be normal. At the day 7 assessment, if a value is missing then we will carry forward the closest previously known value. The GCS component of the SOFA score will be omitted. (See Appendix B)

11. 90-day hospital mortality (any hospital)
12. **Development of ARDS within 7 days:** We will determine the presence and severity of ARDS for each day of assisted ventilation to day 7. For participants on assisted ventilation with P/F <300 or imputed P/F <300, FiO2 ≥40%, and PEEP ≥5 cm H2O, determine if hypoxemia is valid, acute, and not fully explained by CHF or fluid overload. If yes, local investigators will review the first CXR (or CT) performed on each ventilated day with valid P/F or imputed P/F <300 (to day 7). If no chest imaging studies are present that day, site investigators may review available imaging one day before or after to determine if ARDS imaging criteria are met. ARDS imaging criteria are met if the images are consistent with ARDS (bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules). If equivocal, the reviewing investigator will adjudicate with additional investigators.
13. Change in serum creatinine from enrollment to discharge, death, initiation of dialysis, or day 28, whichever occurs first.
14. Major Adverse Kidney Events at 28 days (MAKE28): persistent increase in serum creatinine by 200% from baseline (defined as most recent outpatient creatinine from 24 hours to 365 days prior to admission if available: if not available, lowest in hospital creatinine prior to randomization), need for renal replacement therapy, or death
15. Change in Radiographic Assessment of Lung Edema (RALE) score from enrollment to study day 3 in patients who are receiving assisted ventilation or high flow nasal oxygen at the time of study randomization
16. The safety of intravenous Acetaminophen compared to placebo as measured by daily serum AST, ALT, blood pressure following study drug administration (both arms) and incidence of reported adverse events (both arms)
17. Change in plasma IL-6, plasma IL-8, plasma angiopoietin-2, plasma cell-free hemoglobin, syndecan-1, and plasma cell-free DNA from enrollment to days 2 and 3
18. **90 day all-cause mortality**: We will contact patients at day 90 to ascertain their survival status. This will be done by telephone contact with the patient or family members as well as a review of medical records and publicly available data sources. We will use the national death index as a final check for patients with whom we are unable to confirm their vital status through other means.

2.3 Safety Endpoints

AST and ALT will be measured on days 2, 3, 4, 5, and 7 after study enrollment. We will also collect data daily on potential adverse reactions to Acetaminophen, such as rash and hypersensitivity. If either are present and thought to be due to the study drug, the study drug will be stopped.

2.4 Predictive Biomarker Analysis

We will evaluate the predictive value of baseline plasma CFH (Cell-free Hemoglobin) for identifying who have an improvement in the primary endpoint, the three components of the primary endpoint, 28-day mortality or improvement in renal function as assessed by MAKE28.

2.5 Statistical Analysis Plan

The principal analyses will be intention-to-treat (based upon randomization assignment). A comprehensive statistical analysis plan will be written prior to the un-blinding of the primary and secondary efficacy results.

2.6 Interim Analysis

The DSMB will have the ability to analyze all safety data, including AST/ALT, at any time during the study and stop the study indefinitely for safety reasons. The safety report will include a tabulation of all baseline demographics and physiologic variables as well as on-study variables, including SOFA scores, and all adverse events by randomized groups. For monitoring safety, data on 28-day mortality will be included with 95% confidence intervals for any differences between placebo and the acetaminophen group. In addition, a formal safety analysis will be done after 225 patients are accrued. This report will include an analysis of acetaminophen levels. Trough levels greater than 20 mcg/mL will be evaluated for any relationship to AST/ALT levels. Investigators will recommend protocol modification as needed to the DSMB as part of the safety review.

Based on an interim analysis of the primary efficacy variable, this trial may stop for efficacy or futility of APAP relative to placebo. The stopping rules are based on two stage Haybittle-Peto stopping boundaries [1, 2] with Z=3.4 for early efficacy stopping. We plan one interim look at approximately one half of total enrollment and a final look at full enrollment.

Table 1 below presents the stopping boundaries as a function of the mean difference in the primary efficacy variable favoring active treatment and the one-sided p-value favoring active treatment. **Tables 2** and **3** present the probability of stopping at stage one under the null and alternative hypotheses respectively. As can be seen in Table 2 the probability of stopping early for futility under the null is 10%. Table 3 shows that the probability of stopping early for efficacy under the alternative is also 10%.

Table 1. Stopping Boundaries

n	Futility Bound Mean Difference	Efficacy Bound Mean Difference	Futility Bound P-value	Efficacy Bound P-value
~218	-1.51088	4.01088	0.89986	0.0003369
436	1.63584	1.63584	0.02493	0.02493

Table 2. Stopping probabilities given the null hypothesis

Stage	Futility	Efficacy
1	0.10014	0.00034

Table 3. Stopping probabilities given the alternative hypothesis

Stage	Futility	Efficacy
1	0.00034	0.10014

3. Sub-Group by Treatment Interaction

We will do a sub-group by treatment interaction analysis comparing outcomes in acute COVID-19, defined as a positive diagnostic test for SARS CoV-2 in the prior three weeks and pneumonia as primary site of infection, and COVID-19 negative patients for the primary and secondary efficacy endpoints. The analysis will include a tabulation of the treatment effect in COVID-19 positive patients, the treatment effect in COVID-19 negative patients, and the difference between the treatment effect in these two sub-groups. We will also apply this interaction analysis separately to three demographic factors, gender (male versus female), race (White versus Non-White), ethnicity (Hispanic versus Non-Hispanic) and one additional pre-randomization factors, received acetaminophen (yes versus no).

4. Statistical Methods

Overview

Unless otherwise specified all analyses are intention to treat, comparing the two treatment groups of those randomized to receive Acetaminophen and those randomized to receive placebo.

Unless otherwise specified statistical significance will be indicated by two-sided p-values less than or equal to 0.05 with no adjustment made for multiple comparisons.

Analysis is based on all available data with no imputation of missing data, except as needed to calculate selected derived variables, such as SOFA variables.

The specified use of a Chi-square test may be superseded by use of Fisher's exact test given sparse data.

Primary Efficacy Outcomes

Continuous primary efficacy outcomes will be compared between treatment groups using a t-test.

Binary primary efficacy outcomes will be compared between treatment groups using a Chi-square test.

Secondary Efficacy Outcomes

Continuous secondary efficacy outcomes will be compared between treatment groups using a t-test.

Binary secondary efficacy outcomes will be compared between treatment groups using a Chi-square test.

Subgroup by Treatment Interactions for the Primary and Secondary Efficacy Outcomes

Subgroup by treatment interactions for continuous efficacy outcomes will be assessed by an analysis of variance model including a treatment effect, a subgroup effect, and a subgroup by treatment interaction. Contrasts of the model coefficients will be used to estimate the treatment effect in each level of the subgroup variable.

Subgroup by treatment interactions for binary efficacy outcomes will be assessed by a generalized linear model with a binary distribution function and identity link function. The model will include a treatment effect, a subgroup effect, and a subgroup by treatment interaction. Contrasts of the model coefficients will be used to estimate the treatment effect in each level of the subgroup variable.

With 5 binary subgroup variables and N primary and secondary efficacy outcomes there will be a total of 5xN interaction p-values and 10*N p-values for the treatment effect within each subgroup level and over all p-values a total of 15*N. A Bonferroni multiple comparison adjustment over all 15*N p-values is extremely conservative and would probably eliminate detection of any potentially important findings. We therefore choose to designate this, a prior, an exploratory hypothesis generating analysis consistent with the early development phase of a new intervention, so that any findings would need future confirmation. Thus, we will impose no multiplicity correction and report nominal p-values.

However, acknowledging the implications of multiplicity is also important to help interpret the trial results. Interpretation would depend on the research question of the reader. If the reader is interested in any interaction in one specific outcome, then there are 5 tests to adjust for. If the reader is interested in an interaction for any outcome for one subgroup of concern, then there are N tests to adjust for. If the reader is interested in any interaction for any outcome and subgroup, then there are 5*N tests to adjust for. Readers could use the appropriate Bonferroni correction to control the type 1 error rate for their specific research question.

We will, therefore, present all the results with nominal p-values but also provide explanatory text and Bonferroni critical values consistent with various ways of sub-setting the results to specific research questions.

Safety Outcomes

Adverse events will be categorized by MedDRA system organ class and severity. For each category the proportion of patients having one or mor events will be compared between treatment groups with Fisher's exact test.

Acetaminophen trough levels in the first 100 evaluable patients, will be compared between treatment groups. A patient is "evaluable" if the patient received at least five doses of study drug prior to the day two sample draw, and the day two sample was drawn within 12 hours of administration of the previous dose.

Trough APAP levels will be presented graphically with APAP levels displayed on the vertical axis and elapsed time between starting time of previous dose and trough level sample draw displayed on the horizontal axis. This plot will include superimposed established contours separating safe from unsafe levels [3]. One figure will be presented for patients on active treatment and one for patients on placebo treatment.

New AST or ALT Elevation: defined as post randomization AST or ALT ≥ 10 x the ULN in patients who did not meet this criterion prior to randomization, will be compared between treatment groups using a Chi-square test.

New Hy's Law: defined as post randomization AST or ALT ≥ 3 x the ULN with bilirubin ≥ 2 x the ULN on the same calendar day in patients who did not meet this criterion prior to randomization[4], will be compared between treatment groups using a Chi-square test.

Administration of fluid bolus within 120 minutes of study drug infusion: The number of patients given one or more fluid boluses will be compared between treatment groups using a Chi-square test. In those receiving one or more fluid boluses, the number of study drug doses followed by a fluid bolus in each patient will be compared between treatment groups using the CMH mean score test. The volume of fluid given in the largest fluid bolus in each patient will be compared between treatment groups using a T-test.

New use of vasopressor within 120 minutes of study drug infusion: The number of patients given any new vasopressor will be compared between treatment groups using a Chi-square test. The number of new vasopressors given in each patient will be compared between treatment groups using the CMH mean score test. The maximum administration rate of any new vasopressor in each patient (in norepinephrine equivalents) will be compared between treatment groups using a T-test.

Increased dose of vasopressor within 120 minutes of study drug infusion: The number of patients given one or more increased doses of vasopressors will be compared between treatment groups using a Chi-square test. The number of study drug doses followed by a vasopressor rate increase in each patient will be compared between treatment groups using the CMH mean score test. The maximum vasopressor increase in each patient (in norepinephrine equivalents) will be compared between treatment groups using T-test.

Predictive Biomarker Analysis

We will evaluate the predictive value of baseline plasma CFH for identifying patients who have an improvement in the primary endpoint, the three components of the primary endpoint, 28-day mortality or improvement in renal function as assessed by MAKE28.

We will perform two analyses, one treating baseline plasma cell-free Hgb both as a continuous variable and one treating it as a binary indicator for plasma cell-free Hgb greater than 10 mg/dl in the analysis. The lower limit of detection is 0.00625 mg/dl.

Baseline plasma cell-free Hgb by treatment interactions for continuous efficacy outcomes (primary endpoint, the three components of the primary endpoint) will be assessed by an analysis of variance model including a treatment effect, a Hgb effect, and a Hgb by treatment interaction.

Baseline plasma cell-free Hgb by treatment interactions for binary efficacy outcomes (28-day hospital mortality, improvement in renal function as assessed by MAKE28) will be assessed by a generalized linear model with a binary distribution function and logit link function. The model will include a treatment effect, a Hgb effect, and a Hgb by treatment interaction.

References

[1] Martin, G.S., et al., The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*, 2003. 348: p. 1546-1554.

[2] Haybittle, J.L., Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol*, 1971. 44(526): p. 793-7.

[3] Rumack, B. H., & Matthew, H. (1975). Acetaminophen poisoning and toxicity. *Pediatrics*, *55*(6), 871–876.

[4] Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), July 2009, Drug Safety

Table of Variables

Variable	Category	Scale	Method	Notes
Alive and free of organ support to day 28.	Primary efficacy outcome	Continuous	T-test	
28-day day all-cause all-location mortality	Primary efficacy outcome component	Binary	Chi-square test	
Days free of assisted ventilation to day 28 in the overall cohort and survivors	Primary efficacy outcome component	Continuous	T-test	
Days free of new RRT to day 28 in the overall cohort and survivors	Primary efficacy outcome component	Continuous	T-test	
Days free of vasopressors to day 28 in the overall cohort and survivors	Primary efficacy outcome component	Continuous	T-test	
28-day ventilator-free days	Secondary efficacy outcome	Continuous	T-test	
28-day vasopressor-free days	Secondary efficacy outcome	Continuous	T-test	
28-day new renal replacement-free days	Secondary efficacy outcome	Continuous	T-test	
28-day hospital mortality	Secondary efficacy outcome	Binary	Chi-square test	
28-day ICU free-days	Secondary efficacy outcome	Continuous	T-test	
28-day hospital-free days to discharge home	Secondary efficacy outcome	Continuous	T-test	
28-day duration of ICU stay in survivors and non-survivors	Secondary efficacy outcome	Continuous	T-test	
Initiation of assisted ventilation to day 28	Secondary efficacy outcome	Binary	Chi-square test	
Initiation of renal replacement therapy to day 28	Secondary efficacy outcome	Binary	Chi square test	
Change in Sequential Organ Failure Assessment (SOFA) scores between enrollment and study day 7	Secondary efficacy outcome	Continuous	T-test	
90-day hospital mortality	Secondary efficacy outcome	Binary	Chi-square test	
Development of ARDS within 7 days of randomization	Secondary efficacy outcome	Binary	Chi-square test	
Change in serum creatinine from	Secondary efficacy outcome	Continuous	T-test	

enrollment to discharge, death, initiation of dialysis or 28 days, whichever occurs first				
Major Adverse Kidney Events at 28 days (MAKE28):	Secondary efficacy outcome	Binary	Chi-square test	
Change in the Radiographic Assessment of Lung Edema (RALE) score from enrollment to study day 3 in patients who are receiving assisted ventilation or high flow nasal oxygen at baseline.	Secondary efficacy outcome	Continuous	T-test	
Change in plasma IL-6, plasma IL-8, plasma angiopoietin-2, plasma cell-free hemoglobin, syndecan-1, and plasma cell-free DNA from enrollment to days 2 and 3	Secondary efficacy outcome	Continuous	T-test	
90-day all-cause all-location mortality	Secondary efficacy outcome	Binary	Chi-square test	
Daily serum AST, ALT, blood pressure following study drug administration	Safety outcome	Continuous	T-test	
Hypersensitivity or rash	Safety outcome	Binary	Chi-square test	
AST and ALT measured on study days 0, 2-5, and 7	Safety outcome	Continuous	T-test	Analyze by day
Acetaminophen trough level	Safety outcome	Continuous		
Administration of fluid bolus within 120 minutes of study drug infusion	Safety outcome			This outcome is assessed with three questions on the CRF.
New use of vasopressor within 120 minutes of study drug infusion	Safety outcome			This outcome is assessed with three questions on the CRF.
Increased dose of vasopressor within 120 minutes of study drug infusion	Safety outcome			This outcome is assessed with three questions on the CRF.
Incidence of reported adverse events	Safety outcome	Count	Poisson regression	
Predictive value of baseline plasma CFH by treatment	Predictive Biomarker Analysis	Binary/Continuous	ANOVA and GLM	

Note: The Chi-square test may be replaced by Fisher's exact test if data sparse.