Biomedical Statistical Consulting

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STATISTICAL ANALYSIS PLAN

Version 1.0

January 6, 2020

Product: Reltecimod (AB103)

Protocol Number: ATB-203

Phase 3 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of Reltecimod as compared to placebo in addition to standard of care in patients with sepsis-associated acute kidney injury (SA-AKI)

Development Phase: Phase 3

IND Number: 128,927

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SPONSOR

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Statistical Analysis Plan
Version 1.0, 06 January 2020

Phase 3 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of Reltecimod as compared to placebo in addition to standard of care in patients with sepsis-associated acute kidney injury (SA-AKI)

SIGNATURE OF APPROVAL

Wayne M Dankner 06JAN2020

Wayne M Dankner, MD — Date

Chief Medical Officer

Atox Bio, Ltd

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SIGNATURE OF APPROVAL

Greg Maislin 06 JAN 2020

Greg Maislin, M.S, M.A. Date

Principal Biostatistician

Biomedical Statistical Consulting

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1 Purpose and Scope of SAP

The purpose of this Statistical Analysis Plan (SAP) is to provide details regarding the analyses sets, endpoints, and statistical analysis methods to be used to meet the objectives of this trial. When differences exist in descriptions or explanations in the Clinical Study Protocol and this SAP, the SAP prevails. This SAP will be finalized prior to unblinding of the treatment allocation codes.

This document is designed to be a stand-alone document in terms of conveying essential statistical approaches to the analysis of the data. Additional definitions and details regarding variables collected are provided in the Clinical Study Protocol.

Statistical approaches were developed to be consistent with accepted statistical and clinical trial principles including ICH E9, Statistical Principles for Clinical Trials[1].

[1] ICH E9 Expert Working Group. Statistical Principles for Clinical Trials: ICH Harmonized Tripartite Guideline. Statistics in Medicine 1999; 18:1905–1942.

2 Key Elements of the Analysis Plan

2.1 Primary Efficacy Analysis

2.1.1 Primary Superiority Hypothesis

The primary effectiveness endpoint is ***freedom from durable loss of renal function at Day 28.*** Success requires:

- Alive at Day 28,
- Free of dialysis at Day 28, and
- Less than a 37% loss of estimated Glomerular Filtration Rate (eGFR; measured with the Modification of Diet in Renal Disease (MDRD) formula from the patient's reference eGFR)) at Day 28.

Reference creatinine values, baseline AKI stage and percentage loss of eGFR will be determined through algorithmic determination (see details below). Percentage loss of eGFR determined algorithmically will be based on a comparison of eGFR at screening compared to an algorithmically determined reference creatinine value.

The primary efficacy comparison involves testing the following one-sided superiority hypotheses: **Ho:** $\pi_{0.50} - \pi_{placebo} \leq 0$ **vs Ha:** $\pi_{0.50} - \pi_{placebo} > 0$; where $\pi_{0.50}$ and $\pi_{placebo}$ represent the true probability of freedom from durable loss of renal function at Day 28. Each probability represents the proportion of subjects on each arm expected to achieve complete recovery. These hypotheses will be tested using a one-sided type 1 error rate of α=0.05. The null hypothesis will only be rejected if the investigational drug demonstrates superiority. An unadjusted chi-square test will be used to test this hypothesis.

2.1.2 Sample Size Justification

This trial will enroll 120 subjects randomized in a 1:1 ratio to either Reltecimod 0.5 mg/kg (n=60) or placebo (n=60), both in addition to standard of care (SoC). Sample size analysis was performed assuming all patients will be evaluable for the primary endpoint due to using last observation carried forward (LOCF) for patients missing the creatinine value on Day 28. The primary efficacy hypothesis will be tested using an unadjusted χ^2 statistic with a one-sided α=0.05 significance level. Rejection of the null hypothesis will only occur if investigational drug superiority is demonstrated. Statistical power was computed for a range of expected treatment group differences supported by the results of preliminary studies. The following table summarizes the statistical power for a total sample size of N=120 (60 per group) for various assumptions regarding the success rate in the investigational arm and assuming a success probability of 0.50 among controls. This sample size results in 89% power if the true success rates are 75% and 50% for the investigational drug and placebo, respectively, for a group difference of 25%. Power remains above 80% if the true group difference is at least 22% (Table 1).

Table 1. Computed Power			
Index	**Control**	**AB103**	**Power**
1	0.5	0.65	0.507
2	0.5	0.70	0.727
3	0.5	0.71	0.766
4	0.5	0.72	0.802
5	0.5	0.73	0.834
6	0.5	0.74	0.864
7	0.5	0.75	0.890

2.2 Randomization

120 patients will be recruited into the study and randomized to either 0.5 mg/kg Reltecimod or placebo in a 1:1 ratio. Randomization will be performed within site and according to the following stratification factors:

- **Acuity of AKI:** reflects whether or not AKI is diagnosed at time of presentation of abdominal infection or during the 48 hours following the suspected diagnosis of abdominal infection.

- **Subject Age:** ≥18 to ≤75 and >75 to ≤85 years old

- Four computer-generated, blocked randomization lists will be provided for each site, one for each of the four strata defined on the basis of the 2 by 2 cross-tabulation of the two stratification variables. Within each block, half of the assignments will be to active drug and half to placebo, in random order. Block sizes will be varied.

The following provide details regarding randomization.

Biomedical Statistical Consulting will utilize software written in R Software (acceptable R versions >3.1) to create the randomization schedule. The randomization inputs to this validated software are provided in Exhibit 1, with the exception of the final random seed utilized to generate the blinded randomization schedule. A draft randomization schedule will be generated with clearly marked "dummy" randomization treatment assignment (e.g., 'DUMMY-Placebo' and 'DUMMY-Active'), and then exported to the necessary format for upload into the online randomization and study management system (RAVE Balance RTSM by Medidata Solution) administered by the Sponsor's CRO (PharPoint Research, Inc.). The accurate upload of this "dummy" randomization schedule will then be verified by the unblinded study statistician, following the schedule provided by PharPoint Research, Inc. After verification, the process is repeated by the unblinded study statistician by rerunning the randomization software with updated seeds to determine the final (blinded) randomization schedule, with any "dummy-specific" notation removed. This final (blinded) randomization schedule is then uploaded to the online study management system utilizing the

identical process verified through the "dummy" randomization schedule. A variable indicating the blinded treatment allocations will not be part of the clinical study data to be managed by the data management CRO to avoid risk of unblinding through inadvertent data transfer. Therefore, only blinded study data will be available to the blinded primary study statistician and blinded analysis staff. The randomization schedule parameters were set so that there would be an excess number of potential sites to over at least 60 sites in the US and at least 50 sites in France, Belgium and Netherlands. For every potential site, the maximum number of possible subjects was 30. Block sizes were randomly set to 2 or 4. Within each block, an equal number of allocations were made to the active and placebo groups. Separate randomization schedules were provided for each of 4 strata defined on the baseline of the acuity of AKI diagnosis and age category as described above.

2.3 Analysis Sets

The following analysis sets are defined:

- Intent-to-treat (**ITT**): The ITT analysis set will include all randomized patients.

- As-Treated (**AT**): The AT analysis set will include all randomized patients who were exposed to study medication (active or placebo). The AT analysis set will be used in primary safety analyses with patients assigned to actual treatment received and in supporting effectiveness analyses.

- Modified Intent-to-treat (**mITT**): The mITT analysis set will include patients who were exposed to study medication and who had a definitive diagnosis of abdominal sepsis and Stage 2 or Stage 3 AKI with patients assigned to the treatment actually received. The mITT analysis set may be used in supporting effectiveness analyses if more than a small number of such exclusions are made or more than a small number of patients are not treated with their randomly assigned treatment allocation.

- Per Protocol (**PP**): Optionally, a PP analysis set may be used in secondary effectiveness analyses. The PP analysis set includes patients in the mITT analysis set assigned according to actual treatment received and excluding patients with either: 1) significant violations of inclusion or exclusion criteria with potential to confound treatment effect estimates, or 2) post randomization protocol violations with potential to confound treatment effect estimates. Exclusions from the PP analysis set will be determined based on blinded clinical data. The PP analysis may be further restricted to exclude patients who do not survive at 3 least days when evaluating critical care variables.

2.4 Control of Blinding and iDMC

An independent data monitoring committee (iDMC) will be established to evaluate the safety of the study. A detailed iDMC charter will be provided to clarify all relevant issues relating to firewalls to protect against potential operational biases. The charter will provide decision rules, composition of the iDMC members, and their conflict of interest statements.

The iDMC reviews of the safety data are is planned for after 60 patients (and possibly a second review depending on sample size re-estimation) have completed 28 days of the study.

For each planned iDMC review, all safety data on all patients who received one dose of study drug will be made available to the committee. The data reviewed by the iDMC will be unblinded and presented by treatment group to facilitate recommendations to the Sponsor. Data submitted to iDMC review will be unaudited.

A designated unblinded statistician will provide unblinded safety data to the iDMC using programs constructed and validated by the blinded Study Statistician and Statistical Programming Team.

The iDMC may also meet on an ad-hoc basis when immediate safety concerns arise. Thus, in case of urgency, the chair of the committee could address any questions or concerns regarding the safety of the patients.

As noted above, this study will remain blinded as to treatment allocation. The actual randomized treatment allocations will be kept by an unblinded statistician responsible only for managing the randomization process. The data variable indicating the blinded treatment allocations will not be part of the clinical study data to be managed by the data management CRO. Therefore, only blinded study data will be available to the primary study statistician and responsible primary programming staff.

There are three statisticians in this study with different roles:

- Unblinded study statistician - performs randomization and provides backup
- Unblinded iDMC statistician - independent statistician supporting iDMC operations
- Blinded primary study statistician – primary lead statistician

The role of the unblinded study statistician is:

- Perform final randomization
- Provide the randomization to the pharmacy vendor
- Provide randomized allocations in electronic form to the unblinded iDMC statistician
- Serve as a backup unblinded statistician

A second, unblinded statistician will work with the iDMC to provide unblinded data as necessary for iDMC deliberations. This second, unblinded statistician is from ACI, the CRO responsible for supporting the iDMC.

Analysis staff under the direction of the primary lead statistician, will develop SAS based programs to process clinical data provided by the blinded data management CRO and to populate all planned safety analysis tables and listings. This development phase includes using a pseudo randomization

for purposes of table generation. The programming and relevant data will be provided to the independent unblinded iDMC statistician.

3 Description of variables to be included in statistical analyses

3.1 Medical and Surgical History

A complete medical history identifying both clinically relevant past medical and surgical conditions as well as active medical or surgical conditions will be reported on the Medical History eCRF. All chronic medications will be identified and characterized by trade or generic name, route of administration, as well as reason for use.

Baseline signs and symptoms, or adverse events occurring between signing the informed consent to receiving study drug, should be captured on the Baseline Signs and Symptoms eCRF.

3.2 Physical Examinations

Physical examinations will include a clinically appropriate examination of vital organ systems. These should include at a minimum the cardiovascular, respiratory, abdomen, extremities, and neurologic body systems.

3.3 Interim Physical Examinations (Symptom-Driven)

Interim PE will be targeted to include clinically appropriate examination of specific organ systems based on patient related signs and symptoms.

3.4 Concomitant Medication

All concomitant medications, including ancillary, antimicrobials, immunosuppressant, and nephrotoxic drugs (with the exception of over the counter medications (unless an antimicrobial, immunosuppressant or nephrotoxic drug), vitamins, laxatives, intravenous fluid and electrolyte replacement, parenteral nutrition, topical medications (unless an antimicrobial) and other selected medications as described in the Study Procedure Manual), will be entered into the eCRF and identified by their generic or trade name. Information about antimicrobial medications immunosuppressants, and nephrotoxic drugs should include the dose, dosing frequency, route of administration, duration (start and stop times and dates), and reason for administration (to treat primary or secondary infection or for surgical prophylaxis). Information to be collected about non-antimicrobial medications should include generic or trade name, route of administration, duration (start and stop dates) and reason for administration.

Timing and adequacy of antibiotic therapy (based on institutional guidelines, baseline pathogens and antimicrobial sensitivity) will be reviewed by the Principal Investigator.

3.5 Abdominal Infection and NSTI Type

The type of intra-abdominal process (e.g. complicated appendicitis or diverticulitis, peritonitis due to perforation of the stomach or small or large intestine, gangrenous or necrotic infected bowel or organ; or post-traumatic peritonitis) causing peritonitis and abdominal sepsis will be captured along with the type of surgical or interventional procedure to establish source control. NSTI type will be categorized as Necrotizing Fasciitis, Fournier Gangrene, Gas Gangrene and Other.

3.6 Vital Signs

Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate (spontaneous, assisted or controlled) and temperature. While these data points may be determined many times during the course of the patient's hospitalization, recording vital signs (first set of vitals on that day) in the eCRF will be based on once daily readings for specified time sequences according to time and events (see Appendix A, Section 18.1 of the Clinical Study Protocol).

3.7 Clinical Scores

Clinical scores/criteria components will be collected in the study. APACHE II score criteria will only be collected at screening (see Section 18.2 of the Clinical Study Protocol) while SOFA score will be collected throughout the study (see Section 18.3 of the Clinical Study Protocol). APACHE II will be used to determine disease severity while SOFA score will be evaluated as a secondary clinical endpoint. Individual parameters of the SOFA score will be collected and be correlated to response. All scores will be calculated retrospectively. Data will be recorded in the eCRF at specified time points according to time and events (see Section 18.1 of the Clinical Study Protocol).

3.7.1 SOFA Score Definition

Screening SOFA score: includes measurements of six organ systems (cardiovascular, respiratory, renal, coagulation, GI/hepatic, and CNS) with data values evaluated any time after arrival at study site hospital. *Follow-up SOFA scores*: measurements of (the same) six organ systems with data values measured on Days 1, 3, 7, and 14, and calculated retrospectively.

Where it is not possible to take arterial blood gases to determine the SOFA respiratory parameter, SpO2value can be converted to a PaO2 value to allow calculation of the PaO2/FiO2 ratio.

For this study, the liver component is excluded in the primary total sum score, and the resulting sum score is referred to in this study as 'mSOFA'.

3.7.2 Acute Physiology and Chronic Health Evaluation II (APACHE II)

APACHE II scores measure disease severity and will be obtained at screening. Exploratory stratified analyses will be based on APACHE II scores of greater than or equal to 10 vs. APACHE less than 10.

If there are missing data in the components comprising the APACHE II, then some factors may only be evaluable based on medical judgment. If this is the case, Sponsor will provide completed screening APACHE II scores for each randomized patient and the APACHE II scores will not be considered part of the audited clinical data set provided by the data management CRO.

3.8 Clinical Laboratory Assessments

Safety laboratory investigations will include results of hematology labs (CBC including platelets and white blood cell differential), and of blood chemistry labs (Glucose; Electrolytes (Sodium, Potassium, Chloride, Bicarbonate, Calcium, Phosphorus); Renal function tests (Urea/BUN, Serum Creatinine); Liver function tests (Albumin, Bilirubin Total, Alanine transaminase (ALT), Aspartate

transaminase (AST), Alkaline phosphatase (ALP); Total Protein). Also, urine albumin / creatine ratio will be evaluated.

Pregnancy testing will be done on all women of childbearing potential participating in the study (using the quicker of a blood test or urine test).

Clinical laboratory assessments will be collected at intervals according to time and events in Section 18.1 of the Clinical Trial Protocol.

Hematology will be collected at Screening, Day 1, Day 3, Day 7, Day 14, and Day 29.

Blood chemistry will be collected at Screening, Day 1 (bilirubin and creatinine only), Day 2 (creatinine only), Day 3 (bilirubin and creatinine only), Day 7, Day 10 (creatinine only), Day 14, Day 21 (creatinine only), Day 29 (albumin and creatinine only), 3 to 21 days after Day 29 visit (creatinine only), and at 3 months (creatinine only). The standard C-Reactive Protein (CRP) test (not the high sensitivity-hsCRP) will be used to evaluate inflammatory response and will be obtained at Screening and Days 7, 14, and 29.

Urine will be collected at Screening, Day 1, Day 3, Day 7, Day 14, Day 29 and Month 3 to measure albumin/creatinine ratio to evaluate renal function and potential injury.

3.9 Microbiology

Microbiological testing will be performed as described in the Clinical Study Protocol time and events schedule. Testing will be performed on blood specimens at Screening and intra-abdominal specimens from the first surgical or interventional radiology procedure, respectively.

3.10 Creatinine, AKI, AKD, and eGFR

3.10.1 Reference Creatinine

Exhibit 1 summarizes the algorithmic determination of reference creatinine. The algorithmic determination of baseline AKI stage will be based on comparing screening creatinine to the reference creatinine determined by Exhibit 1.

Note: If there is any discrepancy between the algorithm and the assignment by the site as to reference creatinine then this will generate a medical review which may result in a modified baseline AKI stage different from the algorithmic determination. All such cases will be documented in the clinical study report. Sensitivity analyses will be conducted as needed to evaluate the impact of any modifications from the algorithmic determination.

Exhibit 1. Algorithmic Determination of Reference Creatinine

Preprocessing step:
Creatinine values obtained within 2 days of dosing will be handled as follows:
If there is only one value, this value will be excluded as input to the algorithm below.
If there are more than one value, compare the maximum to the minimum, and if within 25%, then all values will be included as input to the algorithm below. If greater than 25%, then the values obtained within 2 days will be excluded as input to the algorithm below.

This table indicates the rules to be used to determine reference creatinine based on the numbers of historical values available during the last 3 months prior to screening and available 4 to 12 months prior to screening. In general, the algorithm prioritizes use of historical creatinine values obtained within the last 3 months.

Number of last 3 month values	Number of 4 to 12 months	Rule
0	0	Use MDRD to determine reference creatinine.
0	1	Use the 4- to 12-month value.
0	>=2	Use median of 4 to 12 month values.
1	0	Use <= 3-month value.
>=2	>=0	Use median of <= 3-month values.
1	1	Use the mean of the two available values.
1	>=2	Use the median of all available values.
>=2	1	Use the median of all available values.

The SAS code used to implement the MDRD formula[1,2] to determine a reference creatinine when no historical values are available is:

```
if sex='Male' and black=0 then do;
      t1 = der_age**(-0.203) ;
      t2 = 1;
      t3 = 1;
      t4 = 186 * t1 *t2 *t3 ;
      Scrt = (75 / t4 )**(-0.887)  ;
      end;

if sex='Female' and black=0 then do;
   t1 = der_age**(-0.203) ;
      t2 = 0.742;
      t3 = 1;
      t4 = 186 * t1 *t2 *t3 ;
      Scrt = (75 / t4 )**(-0.887)  ;
```

[1] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999 Mar;130(6):461-470.

[2] Levey AS, Greene T, Kusek I, Beck G. A simplified equation to predict glomerular filtration from serum creatinine (Abstract). J Am Soc Nephrol 2000;11:155A]

```
        end;

if sex='Male' and black=1 then do;
        t1 = der_age**(-0.203) ;
        t2 = 1;
        t3 = 1.21;
        t4 = 186 * t1 *t2 *t3 ;
        Scrt = (75 / t4 )**(-0.887)  ;
        end;

if sex='Female' and black=1 then do;
    t1 = der_age**(-0.203) ;
        t2 = 0.742;
        t3 = 1.21;
        t4 = 186 * t1 *t2 *t3 ;
        Scrt = (75 / t4 )**(-0.887)  ;
        end;
```

3.10.2 Screening AKI and Screening eGFR

Screening (pre-dose) AKI will be determined by comparing screening (pre-dose) creatinine to the algorithmic determination of reference as described in Exhibit 1 based on the rules summarized in Exhibit 2.

The screening creatinine is necessary to establish baseline eGFR. However, according to the Clinical Protocol, the AKI stage used to determine eligibility into the study may be determined through urine outcome criteria. If there is any discrepancy between the algorithm and the assignment by the site as to reference creatinine then this will generate a medical review which may result in a modified baseline AKI stage different from the algorithmic determination. However, in all cases, the algorithmic determination will be used when determining eGFR. All such cases will be documented in the clinical study report. Sensitivity analyses will be conducted as needed to evaluate the impact of any modifications from the algorithmic determination in Screening AKI stage.

Exhibit 2. Algorithmic Determination of Screening (pre dose) AKI Stage	
Stage	**Serum Creatinine**
0	<1.5 times reference
1	1.5 to <2.0 times reference
2	≥2 to 3 times reference
3	≥ 3 times reference OR Increase in serum creatinine to ≥4 mg/dL OR Initiation of renal replacement therapy
Reference may be either algorithmically determined or independently adjudicated depending on analysis.	

Screening eGFR will be determined using the following formula.

Screening eGFR (mL/min/1.73 m²) = 175 × (Screening Cr)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American).

3.10.3 Day 28 eGFR

Day 28 eGFR will be determined by converting Day 28 creatinine to Day 28 eGFR using the following formula:

Day 28 eGFR (mL/min/1.73 m²) = 175 × (Cr Day 28)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American).

Percentage loss in eGFR at Day 28 will be determined using the following formula.

Percentage loss in eGFR at Day 28 = 100% times [Screening eGFR - (Day 28 eGFR) / Screening eGFR]. If percentage loss ≥ 37% then patient fails key secondary endpoint.

3.10.4 Day 14 eGFR

Day 14 eGFR will be determined by converting Day 14 creatinine to Day 14 eGFR using the following formula:

Day 14 eGFR (mL/min/1.73 m²) = 175 × (Cr Day 14)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American).

Percentage loss in eGFR at Day 14 will be determined using the following formula.

Percentage loss in eGFR at Day 14 = 100% times [Screening eGFR - (Day 14 eGFR) / Screening eGFR]. If percentage loss ≥ 37% then patient fails the Day 14 endpoint.

3.10.5 Day 90 eGFR

Day 90 eGFR will be determined by converting Day 90 creatinine to Day 90 eGFR using the following formula:

Day 90 eGFR (mL/min/1.73 m²) = 175 × (Cr Day 14)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American).

Percentage loss in eGFR at Day 90 will be determined using the following formula:

Percentage loss in eGFR at Day 90 = 100% times [Screening eGFR - (Day 90 eGFR) / Screening eGFR]. If percentage loss ≥ 37% then patient fails the Day 90 endpoint.

3.10.6 Additional Processing Details

Based on experience gained through processing of AKI endpoints in the recently completed ATB-202 study, the following data processing convention will be employed.

- To account for renal replacement therapy (RRT), the exact dates on which the patient is on dialysis will be determined and compared to the exact date on which the labs were drawn for the creatinine sample. If the sample was drawn within 2 days from RRT start then it was excluded from all analyses.
- If the reference creatinine is greater than 1.4, then all available creatinine values obtained on Day 10 and after, including unscheduled visits, will be evaluated. If the maximum is 1.5x the minimum, then the reference creatinine is replaced by the MDRD.
- LOCF will be used for missing Day 14 creatinine starting from Day 10.
- LOCF will be used for missing Day 28 creatinine starting from Day 7.

3.10.7 Alternative Algorithmic Determination of Day 28 Creatinine

If Day 28 creatinine is missing, LOCF will be used to impute Day 28 creatinine in primary analyses.

As a sensitivity analysis, the following alternative approach to determining the recovery creatinine is as follows.

1. Take all creatinine values between Day 14 and Day 28 and determine if they are consistent –if high and low value in the range are different by >50% (example 1.0 and 1.6) flag as "unstable".
2. If unstable, take the LAST value in the range as the recovery creatinine.
3. If not unstable, take the MEAN of all values in the 14 to 28 day range as the recovery creatinine.

4 Endpoints

4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is ***freedom from durable loss of renal function at Day 28***. The primary effectiveness endpoint requires:

(i) Alive at Day 28,

(ii) Free of dialysis at Day 28, and

(iii) Less than a 37% loss of estimated Glomerular Filtration Rate (eGFR; measured with the Modification of Diet in Renal Disease (MDRD) formula from the patient's reference eGFR)) at Day 28.

Reference creatinine values, baseline AKI stage and percentage loss of eGFR at 28 will be determined through algorithmic determination (see details above). Percentage loss of eGFR determined algorithmically will be based on a comparison of eGFR at screening compared to an algorithmically determined reference creatinine value.

Note: The Clinical Protocol allows subjects to quality for enrollment in terms of AKI stage through urine outcome.

4.2 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints for this study are:

- Freedom from durable loss of renal function at Day 14
- Freedom from durable loss of renal function at Day 90

Reference creatinine values, baseline AKI stage and percentage loss of eGFR at Days 14 and 90 will be determined through algorithmic determination (see details above). Percentage loss of eGFR determined algorithmically will be based on a comparison of eGFR at screening compared to an algorithmically determined reference creatinine value

- Resolution of organ dysfunction (organ resolution is defined as having a total mSOFA score of ≤1) at Day 14
- Resolution of specific organ dysfunction (defined as having an individual organ mSOFA score of ≤1) at Day 14
- Critical care and hospital stay parameters
    - Hospital length of stay
    - ICU length of stay
    - ICU-free days in 28 days
    - Days on ventilator
    - Ventilator free days in 28 days
    - Vasopressor days
    - Vasopressor free days in 28 days
    - Discharge status

- Patient survival at Days 14, 28 and 90.
- Presentation of Stages 1, 2, or 3 AKI (using the KDIGO criteria)
- **Stratifications involving Day 14 mSOFA<=1 vs Day 14 mSOFA>=2**
    - Compare critical care between Day 14 mSOFA<=1 vs Day 14 mSOFA>=2
    - Compare dose groups in those with Day 14 mSOFA<=1
    - Compare dose groups in those with Day 14 mSOFA>=2

- Among patients presenting with cardiovascular failure (shock), dose group predicting Day 14 mSOFA<=1
- Survival to Day 90 as a function of ***freedom from durable loss of renal function at 28*** (overall and by dose group

4.3 Exploratory Effectiveness Endpoints

The following are exploratory endpoints for this study:

- Improvement or freedom from durable loss at Day 14
- Improvement or freedom from durable loss at Day 28
- Improvement or freedom from durable loss at Day 90

- Incidence of chronic kidney disease (CKD) at Day 90 as determined by detection of albuminuria and estimated glomerular filtration rate (eGFR) using CKD-EPI equation
- Urinary albumin/creatinine ratio will be summarized for measurements made at Screening, Day 1, Day 3, Day 7, Day 14, Day 29 and Month 3. The measure is used to assess kidney injury and is a marker of CKD
- CRP will be summarized for measurements made at Screening, Day 7, Day 14, and Day 29, and for changes from Screening to Day 7, Day 14, and Day 29.

- Evaluation of RRT use (i.e., type of RRT)

4.4 Discussion Regarding 'Event-Free Days'

Outcomes like duration of mechanical ventilation and incidence of organ failure may be lower in the group with higher mortality simply because of the competing effect of mortality (Rubenfeld, Angus et al 1999)[3]. Patients who die are not at risk to develop further organ failures or prolonged ventilator dependence. One proposed solution to this problem is to calculate life-support-free days. For example, ventilator-free days can be calculated over a predefined measurement period of (typically) 28 days. Patients who die or are mechanically ventilated longer than this period are assigned zero ventilator-free days for any days on which the patient is not alive or any day beyond the 28 days. All survivors accrue one ventilator-free day for each day after entry into the study that they are both alive and free of mechanical ventilation. By combining mortality and morbidity in one measure, the

[3] Rubenfeld, GD, Angus DC, et al. Outcomes reserach in critical care. Am J Respir Crit Care Med 1999, 160(358-367).

"free-day" outcome avoids the problem of competing mortality. A similar approach will be used to determine ICU-free days and vasopressors-free days.

The 28-day horizon will be used when determining ICU-free days, vasopressor-free days, and mechanical ventilation-free days. ICU time will be calculated using calendar days starting on the day of admission to the ICU and ending on the day of ICU discharge, inclusive.

A vasopressor-free day or ventilator-free day will be defined based on calendar days starting from the day of drug administration. Any day upon which a patient experienced no part of a calendar day on a vasopressor or a ventilator is a ventilator/vasopressors-free day. For example, if the patient was on a ventilator for one hour on any given day, or for even one minute, this day will not count as a ventilator-free day. The same method will be used in calculating vasopressor-free days; a vasopressor-free day means a day alive and not on a vasopressor at any time during that day. This method is a convention generally accepted for these parameters. Events that occur under general anesthesia are not counted. Hospital length of stay will be calculated according the total number of calendar days in the hospital. Where indicated as such in the patient's medical record the hospital discharge date will be recorded as the date when the hospital staff indicate that the patient is 'ready for discharge' (to avoid extending hospital length of stay solely because the patient is waiting to be placed in skilled nursing facility or equivalent setting but had recovered adequately from their illness to meet hospital discharge criteria).

4.5 Safety Endpoints

Adverse events and clinical parameters (HR, BP, vital signs), laboratory parameters (clinical chemistry and hematology), and survival will be evaluated as safety endpoints.

5 Analysis Approaches

5.1 Preliminary and Descriptive Analyses

Descriptive analyses will be performed in order to characterize the treatment groups and to confirm that the randomization resulted in no clinically significant group differences at baseline. Baseline variables will be compared between groups using means, standard deviations, median, minimum and maximum values for continuous variables and counts and percentages for categorical variables. Although emphasis will be on clinical significance, baseline comparisons will include t-tests or Wilcoxon rank sum tests as appropriate for interval variables and chi-square or Fisher's exact tests as appropriate for nominal variables to aid in the screening for baseline differences. Similarly, changes in clinical endpoints over time will be summarized within each treatment group using summary statistics including mean and median change scores, standard deviations and ranges. Pearson or Spearman rank correlation coefficients will be used to characterize associations among variables within treatment group. For time-to-event outcomes (i.e., event-free survival), descriptive analyses will include construction of group specific Kaplan-Meier survival curves as appropriate.

5.2 Primary Endpoint

The primary efficacy comparison involves testing the following one-sided superiority hypotheses: **Ho:** $\pi_{0.50} - \pi_{\mathbf{placebo}} \leq \mathbf{0}$ **vs Ha:** $\pi_{0.50} - \pi_{\mathbf{placebo}} > \mathbf{0}$; where $\pi_{0.50}$ and $\pi_{\mathbf{placebo}}$ represent the true probability of freedom from durable loss of renal function at Day 28. Each probability represents the proportion of subjects on each arm expected to achieve complete recovery. These hypotheses will be tested using a one-sided type 1 error rate of α=0.05. The null hypothesis will only be rejected if the investigational drug demonstrates superiority. An unadjusted chi-square test will be used to test this hypothesis. The corresponding two-sided type 1 error rate is α=0.10. Therefore, the null hypothesis will be rejected if the chi-square p-value is less than 0.10. The corresponding 90% two-sided confidence interval will be provided. The lower bound of the 90% confidence interval is equivalent to the lower bound of a 1-sided 95% confidence interval. Based on the study data, it can be concluded that the true difference in success rates is at least equal to the lower bond of the 1-sided 95% confidence interval.

5.3 Secondary Endpoints

The same analysis as described above will be performed for freedom from durable loss of renal function at Days 14 and 90 and from improvement for freedom from durable loss of renal function as Days 14, 28, and 90.

Additional secondary endpoints include mSOFA over time, critical care and hospital stay parameters (ICU and ICU-free days, ventilator days and –free days, vasopressor days and –free days, and hospital length of stay (LOS)). Analyses for these endpoints will generally be descriptive, with emphasis on characterizing clinical effect sizes. Nominal p-values will be presented. Categorical outcomes will be described using counts and percentages with nominal p-values determined through chi-square or exact methods. Critical care and hospital stay endpoints will be described using non-parametric approaches including using concordance statistics to characterize clinical effect sizes and Wilcoxon rank sum tests to determine nominal statistical significance. Methods appropriate for time-to-event endpoints including survival and life-table methods will be used for time-to-recovery endpoints.

5.4 mSOFA

The Sequential Organ Failure Assessment score or SOFA was originally developed to track a patient's status during a stay in an intensive care unit (ICU)[4,5]. Each of six organ systems are evaluated and assigned ordinal scores from 0 to 4. A total score is the sum of the component scores. For this study, the liver component is excluded from the sum score and the resulting sum score is referred to in this study as 'mSOFA'.

Several approaches will be taken to summarize changes over time and between treatment groups in the clinical scores as described below. Special handling of mSOFA scores includes the following:

1. If an individual organ score is missing but other scores for that day are non-missing, the organ systems that were not evaluated are assumed to be free of organ failure and given a value of zero when determining the sum score.

2. If all organ scores are missing for a specific day, the mSOFA total score from that day will be imputed using LOCF with the following exception, LOCF will not be performed after patient death.

3. When summarizing the individual organ scores apart from the mSOFA total scores, the same rules as above will apply.

Mean values and standard deviations (SD) for the SOFA and for the five specific organ components will be summarized over time with and without LOCF. Similarly, mean change scores from baseline (SD) will be summarized with and without LOCF.

5.5 Assessment of Site to Site Variability in Relative Efficacy

Site to site variability in relative efficacy will be evaluated using a random effects meta-analysis approach using the R package ***metafor*** to implement the analysis. True effects are assumed to be normally distributed with mean μ and variance τ^2. By imposing a specified distribution on the site-to-site variability, i.e. a normal distribution with mean μ and variance τ^2, sensitivity to small sample sizes in individual sites is reduced and the parameters reflecting the magnitude of site-to-site variability are naturally derived. The quantitative measure of the magnitude of heterogeneity is I^2. I^2 is the fraction of $\boldsymbol{\tau^2}$ that is due to effect size heterogeneity, as opposed to sampling variance. Fractions 25% and less are considered small. If there is significant site-to-site variability, the impact on this variability will be evaluated using a random effects logistic regression to test the null hypothesis that the likelihood of achieving freedom from durable loss of renal function at Day 28 is the same for treated and placebo patients accounting for a random site effect.

5.6 Subgroup Analysis

Subgroup analysis will be performed. The following variables will define subgroups.

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[4] Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction failure: On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707–710.

[5] Vincent JL, Angus DC, Artigas A, Kalis A, Basson BR, Jamal HH, Johnson III G., Bernard GR for the PROWESS Study Group. Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. Crit Care Med 2003; 31:834 – 840.

- Stage 2 and Stage 3 AKI
- Acuity of AKI (i.e., whether or not AKI is diagnosed at time of presentation of abdominal infection or surgically confirmed NSTI, or during the 48 hours from the suspected diagnosis of abdominal infection or surgical confirmation of NSTI; developed AKI up to <24 hours or 25 to 48 hours after the suspected diagnosis of abdomianl infection or surgical confirmation of NSTI)
- AKI diagnosed via creatinine criteria vs. urine output criteria
- Abdominal infection or NSTI
- Age ≥18 to ≤75 and >75 to ≤85 years old
- Baseline APACHE II ≥10 and < 10
- Cardiovascular failure yes and no
- Respiratory failure yes and no
- Gender male and female
- Causcasian and other
- BMI category (<30, 30-40, >40)
- Day 14 mSOFA≤1 and Day 14 mSOFA≥2

The following tables will be provided for each subgroup. Results for the primary endpoint will be summarized in a forest plot.

14.2.1.1	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 28 Using LOCF ITT Analysis Set
14.2.2.1	Numbers and Percentages of Subjects Achieving Secondary Freedom from or Improvement in Durable Loss of Renal Function Endpoints at Days 14, 28, and 90 ITT Analysis Set

5.7 Analysis of Other Covariate Effects

Covariates will be assessed for potential confounding (due to lack of perfect randomization balance) or effect modification (subgroup efficacy heterogeneity) using Mantel-Haenszel stratified analyses and/or multiple logistic regression. Covariates will include the set of variables listed above for subgroup analyses. Other baseline variables in which randomization failed to produce balance between groups will be examined in supporting analyses. Covariate effects on estimates and interactions will be assessed to see if there is evidence of efficacy heterogeneity. Results from all subgroups analyses will be considered hypothesis-generating.

5.8 Multiplicity

There is a single primary hypothesis test utilizing a clinical success endpoint, freedom from durable loss of renal function at Day 28. Therefore, there is no issue with regard to multiplicity .

5.9 Descriptive Analyses of Secondary Endpoints

Secondary endpoints have been specified from several domains including critical care and hospital stay parameters (ICU days and ICU-free days, ventilator days and –free days, vasopressor days and –free days, hospital LOS, and clinical systemic parameters (SOFA over time, incidence and recovery from AKI). Analyses for these endpoints will generally be descriptive, with emphasis on characterizing clinical effect sizes[6]. Nominal p-values will be presented as an aid to interpretation. Categorical outcomes will be summarized using counts and percentages with nominal p-values determined through chi-square or exact methods. Critical care and hospital stay endpoints will be described using non-parametric approaches including using concordance statistics (c-stat) to characterize clinical effect size and Wilcoxon rank sum tests to determine nominal statistical significance. Methods appropriate for time-to-event endpoints including survival and life-table methods will be used for time-to-event endpoints.

5.10 Analysis of Event-time and Overall Survival

Time-to-event endpoints will be assessed in descriptive analyses using survival and life table methods as appropriate and illustrated using Kaplan-Meier survival curves[7]. The significance of group will be assessed using logrank statistics.

5.11 Handling of Missing Data

5.11.1 Intent-to-Treat

The purpose of intent-to-treat comparisons is to ensure that randomization is protected (i.e., all groups have comparable baseline characteristics and that any differences besides therapy are due to chance) and to preclude the possibility of bias due to selectively excluding subjects from therapy groups. This is intended to avoid systematic differences among the groups attributable to factors other than therapy assignment[8]. Therefore, we will attempt to include all randomized patients, regardless of intervention or length of follow-up in the primary efficacy comparison.

5.11.2 LOCF of Day 28 and Day 90 Creatinine

In order to determine the primary endpoint, freedom from durable loss of eGFR at Day 28, creatinine is necessary. Patients surviving to Day 28 or later but with missing Day 28 creatinine will have their Day 28 creatinine values determined through LOCF. The same procedure will be used for Day 90 Creatinine.

5.11.3 mSOFA Scores

mSOFA scores over time will be assessed as 1) observed cases, and 2) LOCF.

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[6] Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). New York, Academic Press.

[7] Kaplan EL and Meier P. Nonparametric estimation from incomplete observations, *Journal of the American Statistical Association*, **53:**457-481, 1959

[8] Knickerbocker R. Intent-to-Treat Analyses. In: Chow S-C, ed. *Encyclopedia of Biopharmaceutical Statistics*. Marcel Dekker; 2000.

Individually missing mSOFA component values due to non-measurement are conventionally assumed as normal and this convention will be followed for this study.

LOCF will not be applied to missing mSOFA scores after patient death in analyses that employ LOCF to describe mean values of time. Therefore, analysis of mSOFA mean values using LOCF will focus on morbidity rather than mortality. Also, LOCF will not be used for missing mSOFA after Day 14.

In categorical analyses including formulation of the secondary effectiveness endpoint, total mSOFA score at Day 14 $\leq$ 1, LOCF is necessary to guarantee that every patient has a value at Day 14. LOCF will not be performed after patient death.

5.12 Prior and Concomitant Medication

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either prior or concomitant and will be recorded up to Day 29. If the start and/or stop dates of medications are missing or partially missing, the dates will be compared as far as possible with the date of administration of study drug. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study medication will be classified as prior only.

A medication will be regarded as concomitant if it started on or after the date of first dose of study treatment.

A medication will be regarded concomitant if:

- it started prior to date of first dose of study treatment but was ongoing at the time of the first dose of study treatment.
- the start date of medication is completely unknown.

Medications are coded prior to delivery of the validated clinical data base. The following describes this process.

Drugs are coded to the WHO Drug entry that best represents (most accurately and specifically) the reported term. If a reported term is a trade name, then it will generally be coded to the trade name entry in WHO Drug that contains the correct active ingredients for that trade name. If a reported term is a generic name, then it will generally be coded to the generic entry in WHO Drug with that ingredient or combination of ingredients.

A WHO Drug entry may have one or more ATC (Anatomic-Therapeutic-Chemical) codes assigned to it within the dictionary. If a WHO Drug entry has only one ATC code, then that ATC code is additionally returned for that WHO Drug entry. If a WHO Drug entry has more than one ATC code assigned, then a single ATC code is selected based on the most common usage for the drug and the selected ATC code is additionally returned for the WHO Drug entry.

Separate sets of tables will be provided for non-antimicrobial or non-nephrotoxic medications, antimicrobial medications, and nephrotoxic medications.

6 Safety Analysis

The primary safety measures are AEs (including SAEs), deaths, clinical safety laboratory, PE, and vital signs through Day 29 including determination of survival through Day 29.

The safety profiles will be compared between active and placebo groups using descriptive statistics as appropriate for continuous and categorical safety variables. Changes in continuous safety measures such as laboratory values will be summarized by mean changes over time using descriptive statistics (sample size (N), mean, SD, median, minimum and maximum). The presence of clinically significant safety findings will be summarized by shift tables separately for each group using counts and percentages. AEs will be classified according to system organ class and preferred term and summarized by counts and percentages separately for those recorded on Day 0 (prior to drug administration) and those with onset on Day 1 or later. AEs will also be summarized by relationship to study drug, severity, and whether they are serious. Specific summaries will involve AEs and SAEs in the Infection/Infestation system organ class. Vital signs including weight, temperature, systolic BP, diastolic BP, respiration rate, and heart rate will be summarized across time (Day 0, Day 1, Day 2, Day 3, Day 7, Day 10, Day 14, Day 21 and Day 29) and separately by treatment group by N, Mean, and SD.

6.1 Adverse Events

Treatment emergent adverse events (TEAEs) are defined as those with onset on Day 1 or later. TEAEs will be classified according to system organ class and preferred term and summarized. by counts and percentages. TEAEs will also be summarized by relationship to study drug, severity, and whether they are serious. AE recorded prior to study drug administration will be included in listings but not included in summary tables.

6.2 Laboratory Values

6.2.1 Description of Value Over Time

Laboratory values over time including blood chemistry and hematology will be summarized using descriptive statistics and compared between treatment groups. Values over time and changes over time will be summarized.

6.2.2 Laboratory Shift Tables

The presence of clinically significant changes in laboratory values will be further evaluated using shift tables for blood chemistry and blood hematology changes from screening to Day 7 and from screening to Day 14. These tables will summarize the numbers and percentages of patients that went from a lab value in the normative range at screening to one that is in the higher than normal range or lower than normal range.

6.2.3 Treatment of Clinical Laboratory Abnormalities

Deterioration as compared to baseline in protocol mandated laboratory values, vital signs and other safety variables will only be reported as AEs only if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational medical product. However, the Investigator may record such findings as an AE at his/her discretion in addition

to completing an unscheduled laboratory/vital signs eCRF with the information on the clinically significant test abnormality. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a PE, dermal examination or lung auscultation as compared with the baseline assessment will be reported as an AE. Clinically relevant deterioration in unscheduled assessments of laboratory or vital sign parameters should be reported on additional eCRF pages.

Wherever possible, the reporting Investigator uses the higher level medical concept, rather than the laboratory term (e.g., anemia versus low hemoglobin value).

Additionally, for blood chemistry and blood hematology, results at each visit will be summarized according the frequency of “Critical High”, “Above”, “Within”, “Below”, and “Critical Low” results.

6.3 Physical Exams

Physical exam data on Days 1, 7, and 10 will be summarized in patient specific listings.

6.4 Vital Signs

Vital signs including weight, temperature, systolic BP, diastolic BP, respiration rate, and heart rate will be summarized across time (Day 0, Day 1, Day 2, Day 3, Day 7, Day 10, Day 14, Day 21, and Day 29), separately by treatment group using N, Mean, and SD. Vital signs will be summarized for the Safety Analysis Set.

7 Presentation of Enrollment and Baseline Characteristics

7.1 Site Specific Numbers of Patients by Analysis Set

Table 14.1.1.1 summarizes the numbers of patients screened and for each analysis set by site.

Table 14.1.1.2 summarizes the numbers of patients by site, analysis set, and treatment group.

Table 14.1.1.3 summarizes the numbers of patients by site, treatment group, and randomization stratum in the mITT Analysis set. The primary efficacy analyses will be performed in the mITT analysis set.

Randomization strata are defined as follows:

- **Acuity of AKI:** whether or not AKI is diagnosed at time of presentation of abdominal infection or during the 48 hours following the suspected diagnosis of abdominal infection.
- **Subject Age :** ≥18 to ≤75 or >75 to ≤85 years old.

Table 14.1.1.4 provides the same summary for the As Treated (primary Safety) analysis set.

Table 14.1.1.5 provides the same summary for the PP (secondary efficacy analysis set).

Totals across all sites will be provided for these tables.

7.2 Demographic and Baseline Characteristics of Cohorts

Demographic and baseline characteristics for each analysis set are summarized in Tables 14.1.2.1, 14.1.2.2, and 14.1.2.3 for the mITT (primary efficacy), AT (safety), and PP (secondary efficacy) analysis sets, respectively. The same table is provided for the ITT (randomized) analysis in order to evaluate baseline covariate balance achieved through randomization (Table 14.1.2.4).

Tables 14.1.3.1, 14.1.3.2, and 14.1.3.3 summarize the numbers of patients overall and by treatment group, age category, and gender, for the mITT, AT, and PP analysis sets respectively.

Prior and concomitant medication, lifetime and current medications, and surgical history will be summarized for the Safety (AT) analysis set as are all Safety endpoints. Primary and secondary efficacy endpoints are summarized for the Primary Efficacy (mITT) analysis set.

7.3 Baseline Microbiology

Table 14.1.3.4 summarizes pathogens in blood cultures and surgical samples in the ITT analysis set overall and by treatment group. Table 14.1.3.5 summarizes pathogen (genus / species) in blood culture specimens. Table 14.1.3.6 summarizes pathogen (genus / species) in intra-abdominal or debridement specimens. The data used will be based on verbatim text.

7.4 Prior and Concomitant Medication

. For all prior and concomitant medication tables, the drug class will be capitalized, and the generic drug name will be listed in small letters. The following is an example for the drug class 'corticosteroids'.

CORTICOSTEROIDS
fluticasone
fluticasone propionate
hydrocortisone

All drug classes and all generic drug names will be reported in summary tables and in patient listings. Nephrotoxic drugs as defined in the Appendix 7.

Table 14.1.4.1 will summarize the numbers (%) of patients with prior non-antimicrobial or non-nephrotoxic medications by category and by specific medication.

Table 14.1.4.2 will summarize the numbers (%) of patients with prior antimicrobial medications by category and by specific medication.

Table 14.1.4.3 will summarize the numbers (%) of patients with prior nephrotic medications by category and by specific medication.

Tables 14.1.4.4, 14.1.4.5 and 14.1.4.6 will provide the same summaries for concomitant medications.

7.5 Medical and Surgical History

Table 14.1.5.1 will summarize the numbers and percentages of patients that experienced medical conditions during their lifetime by body system and specific medical conditions when experienced by more than one patient in either group.

Table 14.1.5.2 will summarize the numbers and percentages of patients with current medical conditions by body system and specific medical conditions when experienced by more than one patient in either group.

Table 14.1.6.1 will summarize the numbers and percentages of patients that underwent specific surgical procedures at any time during their lifetime summarized body system and specific surgical procedures.

Table 14.1.6.2 will summarize the numbers and percentages of patients with specific types of surgical or interventional procedures to establish source control and location of source control.

Table 14.1.6.3 will summarize the numbers and percentages of patients according to acuity of AKI,, whether or not a reference pre-infection creatinine value was used, and whether the diagnosis of AKI was based on creatinine alone, urine outcome alone, or both..

7.6 Drug Administration and Timing

Drug administration and timing will be performed for two sets of subjects separately.

- Patients presenting with abdominal sepsis or NSTI and AKI are to have drug administered within 6 hours of decision to go to abdominal surgery or interventional radiology procedure, or surgical confirmation of NSTI.
- Patients who present just with abdominal infection or NSTI and then followed for development of AKI are to have drug administered within 6 hours of diagnosis of AKI

Time to drug allocation, drug administration time point (during, or after surgery), and the actual volume of drug infused will be described in Table 14.1.7.1.

7.7 Patient Disposition and End of Study Status

Table 14.1.8.1 summarizes Day 29 study status by treatment group.

8 Presentation of Efficacy Results

8.1 Primary AKI Endpoint

The numbers and percentages of patients in each group meeting the primary efficacy endpoint of complete recovery (***freedom from durable loss of renal function at Day 28*** is summarized in Table 14.2.1.1 for the mITT (primary efficacy) analysis set. This table also includes the statistical significance of this endpoint based on an unadjusted chi-square statistic. Study success requires one-sided $p \leq 0.05$ for this endpoint which is equivalent to a two-sided $p \leq 0.10$ as long as the percentage of subjects achieving the endpoint is larger in the actively treated group compared to placebo. This table also provides the estimated treatment group difference and 90% confidence interval corresponding to the one-sided significance level. The lower bound of the 90% confidence interval is equivalent to the lower bound of a 1-sided 95% confidence interval. Based on the study data, it can be concluded that the true difference in success rates is at least equal to the lower bond of the 1-sided 95% confidence intervals. Table 14.2.1.1 also provide the same summaries for the components of the primary endpoint.

- Alive at Day 28,
- Free of dialysis at Day 28, and
- Less than a 37% loss of estimated Glomerular Filtration Rate (eGFR; measured with the Modification of Diet in Renal Disease (MDRD) formula from the patient's reference eGFR) at Day 28.

Table 14.2.1.2, and 14.2.1.3 repeat these analyses in the AT and PP analysis sets, respectively.

8.2 Evaluation of Site Heterogeneity in Primary Endpoint Treatment Effects

Table 14.2.1.4 provides comparisons of the percentages of patients achieving the primary efficacy endpoint by site, overall and by treatment group in the mITT analysis. If needed, site-to-site heterogeneity will be evaluated with these data using a random effects meta-analysis approach as described above.

8.3 Secondary and Exploratory AKI Recovery Endpoints

Table 14.2.2.1 summarizes treatment group comparisons based on secondary AKI recovery endpoints in the mITT analysis set including:

- Freedom from durable loss of renal function at Day 14
- Freedom from durable loss of renal function at Day 90
- Improvement or freedom from durable loss at Day 14
- Improvement or freedom from durable loss at Day 28
- Improvement or freedom from durable loss at Day 90

Tables 14.2.2.2 and 14.2.2.3 repeat these comparisons in the AT and PP analysis sets, respectively.

8.4 mSOFA Scores

Table 14.2.4.1 summarizes observed modified total score, organ specific scores, and mSOFA total scores at Screening, Day 1, Day 3, Day 7, and Day 14.

Table 14.2.4.2 provides the same summary after application of last-value-carried forward (LOCF). LOCF was not applied after patient death.

Table 14.2.4.3 summarizes mSOFA at Screening and changes from Screening to Day 1, Day 7, and Day 14 for observed cases.

Table 14.2.4.4 provides the same summary after application of LOCF.

Table 14.2.4.5 summarizes the percentages of subjects with resolution of organ dysfunction (organ resolution is defined as having a total mSOFA score of ≤1) at day 14 and the resolution of specific organ dysfunction defined as having an individual organ SOFA score of ≤1 at Day 14.

8.5 Critical Care and Hospital Stay Parameters, to be Measured until Day 28

The following critical care and hospital stay parameters will be assessed.

- Hospital length of stay (days)
- ICU free days
- Days in ICU
- Days on ventilator
- Ventilator free days
- Vasopressors days
- Vasopressors free days
- Discharge status

Because of the expected skewness in the distributions of these parameters, non-parametric Wilcoxon rank sum tests will be used assess the nominal statistical significance of treatment group differences in these parameters. Table 14.2.5.1 will provide summary statistics by treatment groups including N, mean, median, standard deviation, and minimum, and maximum values.

Table 14.2.5.2 summarizes hospital discharge status.

Table 14.2.5.3 summarizes hospital readmissions.

Table 14.2.5.4 will summarize critical care and hospital stay parameters over days 1 to 28 comparing by primary effectiveness status (success versus failure).

Table 14.2.5.5 will summarize critical care and hospital stay parameters over days 1 to 28 comparing subjects with Day 14 mSOFA≤1 versus Day 14 mSOFA≥2.

Table 14.2.5.6 provides the same information as in Table 14.2.5.6 but for the PP analysis set.

Tables 14.2.5.7 and 14.2.5.8 provide the same information as Tables 14.2.5.1 and 14.2.5.6 but restricted to subjects alive at Day 14.

8.6 Time-to-Event and Survival Analyses

Tables 14.2.6.1 and 14.2.6.2 provide life table analyses for mortality to Day 90 in the Reltecimod and Placebo groups, respectively in the mITT analysis set. Tables 14.2.6.6 and 14.2.6.7 repeat these analyses in the PP analysis set. Tables 14.2.6.3, 14.2.6.4, and 14.2.6.5 provide life table analyses for mortality to Day 90 for subjects randomized to Reltecimod, Placebo, and for both groups, respectively, among subjects achieving Freedom from Durable Loss of Renal Function at Day 28. Kaplan-Meier survival curves will be provided for each of these analyses with cumulative mortality plotted on the y-axis.

8.7 CRP

Table 14.2.7.1 summarizes CRP (standard test, not high sensitivity-hsCRP) at Screening and at Days 7, 14 and 29 and changes from Screening.

8.8 Subgroup Analysis

As noted in Section 5.6, the following variables will define subgroups.

- Stage 2 and Stage 3 AKI
- Acuity of AKI (i.e., whether or not AKI is diagnosed at time of presentation of abdominal infection or surgically confirmed NSTI, or during the 48 hours from the suspected diagnosis of abdominal infection or surgical confirmation of NSTI; developed AKI up to <24 hours or 25 to 48 hours after the suspected diagnosis of abdomianl infection or surgical confirmation of NSTI)
- AKI diagnosed via creatinine criteria vs. urine output criteria
- Abdominal infection or NSTI
- Age ≥18 to ≤75 and >75 to ≤85 years old
- Baseline APACHE II ≥10 and < 10
- Cardiovascular failure yes and no
- Respiratory failure yes and no
- Gender male and female
- Causcasian and other
- BMI category (<30, 30-40, >40)
- Day 14 mSOFA≤1 and Day 14 mSOFA≥2
- Selected baseline pathogen type

The following tables will be provided for each subgroup. Results for the primary endpoint will be summarized in a forest plot.

14.2.1.1	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 28 Using LOCF

	ITT Analysis Set
14.2.2.1	Numbers and Percentages of Subjects Achieving Secondary Freedom from or Improvement in Durable Loss of Renal Function Endpoints at Days 14, 28, and 90 ITT Analysis Set

9 Presentation of Safety Evaluations

9.1 Adverse Events

Treatment-emergent AEs (TEAE) reported during the study will be summarized by treatment group according to Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). Incidence rates of TEAE will be tabulated by class. The distributions of severity will be provided for drug-related AEs, separately by treatment group. Further tabulations by relationship and severity of AE may be provided.

9.1.1 Summary of adverse events

All analyses of adverse events will be based on the As Treated (Safety) Analysis Set. A summary of the numbers and percentages of patients within each treatment group experiencing at least one TEAE will be provided in Table 14.3.1.1. TEAEs will be defined as an AE occurring from Day 1 to end of study which is defined as Day 28. 'Drug-related' is defined as 'possibly', 'probably', or 'definitely' caused by the study medication.

The AE endpoints summarized in this table are:

- With one or more TEAE
- With one or more drug-related TEAE
- With one or more serious TEAEs
- With one or more serious drug-related TEAE
- With one or more severe TEAE
- With one or more moderate or severe TEAE
- TEAE with outcome of death
- TEAE with outcome of drug related death
- Discontinued study drug due to AE/SAE
- Discontinued from study due to AE/SAE

9.1.2 Specific adverse events

The incidence rates (%) and event counts of TEAEs by system organ class (SOC) and by preferred term (PT) will be summarized by treatment group in Table 14.3.1.2. This table will be organized so that SOCs are reported in upper case letters and PT's are reported in lowercase.

Table 14.3.1.3 will summarize the incidence rates (%) of specific TEAE PTs, sorted by descending incidence of PT in the active drug group.

The incidence rates (%) and event counts of drug-related TEAEs by SOC and by PT will be summarized by treatment group in Table 14.3.1.4.

The incidence rates (%) and event counts of serious drug-related TEAEs by SOC and by PT will be summarized by treatment group in Table 14.3.1.5.

Table 14.3.1.6 will summarize the incidence rates (%) of serious TEAE PTs, sorted by descending incidence of PT in the active drug group.

The incidence rates (%) and event counts of serious drug-related TEAEs by SOC and by PT will be summarized by treatment group in Table 14.3.1.7.

9.1.3 Severity of adverse events

The incidence rates (%) and event counts of severe TEAEs by SOC and by PT will be summarized by treatment group in Table 14.3.1.8.

Table 14.3.1.9 will summarize the incidence rates (%) of severe TEAE PTs, sorted by descending incidence of PT in the active drug group.

Counts of drug-related TEAEs in the active drug group will be summarized by severity, SOC and PT in Table 14.3.1.10. Similarly, counts of drug-related TEAEs in the placebo group will be summarized by severity, SOC and PT in Table 14.3.1.11.

9.1.4 Day 0 Adverse Events

A listing will be provided contain any events that occur prior to drug administration.

9.1.5 Safety listings

The following listings will be provided for all patients in the Safety Analysis Set. Adverse event listings will include SOC, PT, relationship, severity, onset and resolution dates, and action taken.

		AE Listings
1	16.2.7.1	All TEAEs Sorted by Specific AE: Day1+ by Treatment Group, Sorted by SOC and PT As Treated (Safety) Analysis Set
2	16.2.7.2	All TEAEs Sorted by Specific AE: Day1+ by Treatment Group, Sorted by Patient ID and Onset As Treated (Safety) Analysis Set
3	16.2.7.3	Drug-Related TEAEs Sorted by Specific AE: Day1+ by Treatment Group, Sorted by SOC and PT As Treated (Safety) Analysis Set
4	16.2.7.4	Serious TEAEs Sorted by Specific AE: Day1+ by Treatment Group, Sorted by SOC and PT As Treated (Safety) Analysis Set
5	16.2.7.5	Serious Drug-Related TEAEs Sorted by Specific AE: Day1+ by Treatment Group, Sorted by SOC and PT As Treated (Safety) Analysis Set
6	16.2.7.6	All TEAEs with Outcome of Death Sorted by Specific AE: Day1+ by Treatment Group, Sorted by SOC and PT As Treated (Safety) Analysis Set
7	16.2.7.7	All TEAEs with Outcome of Drug-Related Death Sorted by Specific AE: Day1+ by Treatment Group, Sorted by SOC and PT As Treated (Safety) Analysis Set

		AE Listings
8	16.2.7.8	All TEAEs with Outcome of Study Drug Discontinuation Sorted by Treatment Group, SOC, and PT As Treated (Safety) Analysis Set
9	16.2.7.9	All TEAEs with Outcome of Discontinuation from Study Sorted by Treatment Group, SOC, and PT As Treated (Safety) Analysis Set

9.2 Clinical Laboratory Assessments

9.2.1 Blood Chemistry

Table 14.3.2.1 summarizes the values and changes from screening (baseline) for each of 15 tests included in the chemistry panels at Screening, Day 7 and Day 14.

Table 14.3.2.2 provides a shift table summarizing the numbers and percentages of patients going from a normal blood chemistry value to a normal, low or high value at Day 7; going from a low baseline blood chemistry value to normal, low or high at Day 7; and going from a high baseline blood chemistry value to normal, low or high at Day 7. The percentages presented in this table correspond to each baseline status. For example, the one of the reported percentages will indicate the percentage of subjects that started with a normal value but ended with a high value. This will be done separately for each treatment group.

Table 14.3.2.3 provides the same information but for shifts to Day 14.

Table 14.3.2.4 provides a summary of blood chemistry frequencies by visit with respect to normal ranges and critical values by treatment group.

Table 14.3.2.5 provides a summary of creatinine values at screening and at Days 1, 2, 3, 7, 10, 14, 21, 29, and 90 by treatment group.

9.2.2 Hepatic Safety

The chemistry data will be evaluated for any cases of Hy's Law or Drug Induced Liver Injury (DILI). These were defined as patients with ALT more than 3 X ULN, Total Bilirubin >2 X ULN with a normal Alkaline Phosphatase. Table 14.3.2.6 summarizes these results.

9.2.3 Blood Hematology

Similarly, Table 14.3.3.1 summarizes the values and changes from baseline for each of the 15 tests included in the hematology panels at Screening, Day 1, Day 3, Day 7, Day 14, Day 29 by treatment group.

Table 14.3.3.2 provides a shift table summarizing the numbers and percentages of patients going from a normal blood hematology value to a normal, low or high value at Day 7; going from a low baseline blood hematology value to normal, low or high at Day 7; and going from a high baseline blood hematology value to normal, low or high at Day 7. The percentages presented in this table correspond to each baseline status. For example, one of the reported percentages will indicate the percentage of subjects that started with a normal value but ended with a high value. This will be done separately for each treatment group.

Table 14.3.3.3 provides the same information but for shifts to Day 14.

9.3 Urinary Albumin/Creatine Ratio

Table 14.3.4.1 summarizes urinary albumin/creatinine ratio at Screening, Day 1, Day 3, Day 7, Day 14, Day 29 and Month 3 and changes in albumin/creatinine ratio. The measure is used to assess kidney injury and is a marker of CKD.

9.4 Incidence of Chronic Kidney Disease (CKD) at Day 90

Table 14.3.4.2 summarizes the incidence of chronic kidney disease (CKD) at Day 90 in the As Treated (Safety) Analysis Set by treatment group. The definitions provided in Appendix 8 will be sued.

9.5 Vital Signs

Baseline height (cm), weight (kg), and BMI (kg/m^2) are summarized for the As Treated (Safety) analysis set in the Demographics and Baseline Disease Characteristics, Table 14.1.2.2.

The following vital sign variables are summarized by treatment group at screening and then at Days 1, 2, 3, 7, 14, 21, and 28 in Table 14.3.5.1. For follow-up visits, changes from screening are also summarized: Weight (kg), Temperature (Celsius), Systolic BP (mmHg), Diastolic BP (mmHg), MAP, Respiratory Rate (breaths/min), and Heart Rate (beats/min).

9.6 Physical Examinations

Results from physical examinations will be provided in the patient listings.

10 Deviations from the Original Statistical Plan

Any deviations from the original statistical plan will be described and justified in the final report.

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12 Appendix 2: AE Listings

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13 Appendix 3: Patient Listings

		Patient Listings
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14 Appendix 5: Study Visits and Procedures

Visit	1 Screening[a]	2 Day 1	3 Day 2	4 Day 3	5 Day 7 ±1 day	6 Day 10 ±1 day	7 Day 14 ±1 days	8 Day 21 ±1 days	9 Day 29 +3 days	10 3 months ±5 days
Informed Consent	X									
Demographics	X									
Medical History	X									
Concomitant Medications[b]	→	→	→	→	→	→	→	→	→	
Weight & Height[c]	X				X		X		X	
Fluid Balance (input/output)	→	→	→	→	→					
Detailed Urine Output[d]	→	→	→	→	→					
Vital Signs[e]	X	X	X	X	X	X	X	X	X	
Physical Examination (PE)	X				X		X			
Interim PE (symptom-driven)		X		X		X				
Baseline Signs & Symptoms[f]	X									

[a] Screening period can be 48 hours after suspected diagnosis of abdominal sepsis
[b] See Section **Error! Reference source not found.** for instruction on level of detailed information required for recording concomitant medications
[c] Height will be taken only at screening or first time that patient height can be measured
[d] Urine output is required for Days 1-7 (while the patient is in the ICU or step-down unit (or equivalent); patients on a general ward only monitor urine output if a Foley catheter is in place as part of standard of care) to assess for development or resolution of acute kidney injury
[e] Systolic & diastolic blood pressure, mean arterial pressure, heart rate, respiration rate, temperature; (first set of vitals on that visit day)
[f] Adverse events reported from ICF signature to Reltecimod administration

Visit	1 Screening[a]	2 Day 1	3 Day 2	4 Day 3	5 Day 7 ±1 day	6 Day 10 ±1 day	7 Day 14 ±1 days	8 Day 21 ±1 days	9 Day 29 +3 days	10 3 months ±5 days
Blood Chemistry[g]	X[h]	X[i]	X[j]	X[i]	X	X[j]	X	X[j]	X[k]	X[j]
Spot Urine Albumin/ Creatinine[l]	X	X		X	X		X		X	X
Standard C-Reactive Protein[m]	X				X		X		X	
Blood Hematology[n]	X	X		X	X		X		X	
Pregnancy Test (if applicable)[o]	X									
Serum for Immunogenicity[p]	X						X		X	X
Urine and Plasma for Storage[q]	X		X		X					
Systemic Inflammatory Biomarkers	X	X	X	X						

[g] Glucose; Electrolytes - Sodium, Potassium, Calcium; Phosphorus, Chloride, Bicarbonate; Renal function tests – Urea/BUN, Creatinine; Liver function tests – Albumin, Bilirubin Total, Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP), Protein Total. In case of abnormal results at the end of the study the results should be followed by the investigator until the abnormalities are resolved or determined as stabilized

[h] If AKI diagnosis not established at time of initial evaluation for abdominal sepsis, then obtain creatinine every 6 hours for up to 48 hours after suspected or confirmed diagnosis of abdominal sepsis to identify development of AKI

[i] Only creatinine and bilirubin

[j] Only creatinine

[k] Creatinine and albumin only

[l] Obtain urine specimen for spot albumin/creatinine ratio. First morning void is preferred

[m] Use standard CRP test (do not use cardiac or high-sensitivity CRP)

[n] Complete blood count including platelet count and white blood cell differential

[o] Preferably the fastest pregnancy test method (urine or blood)

[p] 6 mL blood for serum for storage (for immunogenicity testing) at screening, Days14 and 29, and Month 3

[q] Obtain 5 ml urine and 5 ml blood for plasma for storage for AKI biomarker analysis. Second sample to be collected 24±6 hours (Day 2) after study medication administration. Final sample to be obtained at Day 7

Visit	1 Screening[a]	2 Day 1	3 Day 2	4 Day 3	5 Day 7 ±1 day	6 Day 10 ±1 day	7 Day 14 ±1 days	8 Day 21 ±1 days	9 Day 29 +3 days	10 3 months ±5 days
• RNA[r] • Cytokines / Chemokines[s]	X	X	X	X						
Arterial Blood Gases (if applicable)	X	X		X	X		X			
SpO2 and FiO2 (if arterial blood gases not indicated or unable to obtain)	X	X		X	X		X			
Peritoneal Fluid, Tissue or Abscess Fluid for Microbiology	X									
Inclusion & Exclusion[t]	X									
Randomization	X									
Reltecimod / Placebo Administration		X								
Blood Culture[u]	X									

[r] 5 ml (2 x 2.5 mL) of whole blood to be collected at screening, Day 1 at 4 to 6 hours post-dose, Day 2 at 24 ±4 hours post dose, Day 3 at 48 hours ±4 hours post-dose, and Day 4 72 ±4 hours post dose. Complete blood count with white blood cell differential to be obtained at same time of whole blood for genomic profile sample

[s] Systemic Biomarkers will be taken at screening, 4 to 6 hours, 24±4, 48±4 and 72±4 hours post drug administration; However, if practical consideration allow collection of fewer plasma samples, this will not be considered a protocol deviation. Systemic blood inflammatory biomarkers will include serum cytokines or chemokines such as (but not limited to): IL-6, IL-8, INF-γ, TNF-α, IL-17A, IL-3 and RANTES.

[t] Should be verified twice: a full list of criteria will be verified once before instructing the pharmacist to prepare study drug and a second time immediately before study drug administration according to a partial list to include verification that 6 hours has not elapsed from time to study drug administration

Visit	1 Screening[a]	2 Day 1	3 Day 2	4 Day 3	5 Day 7 ±1 day	6 Day 10 ±1 day	7 Day 14 ±1 days	8 Day 21 ±1 days	9 Day 29 +3 days	10 3 months ±5 days
Adverse Events / Serious Adverse Events[v]	[w] →									
Collect Data on Acute Renal Replacement Therapy	→									
Record any Follow-up Surgical or Interventional Radiologic Procedures for Previously Documented Abdominal Infection		X	X	X	X	X	X			
Evaluation of Adequacy of Antimicrobial Treatment				X						
Critical Care and Hospital Stay Parameters[x]	→									
SOFA Score[y]	X	X[z]		X	X		X			

[u] Blood culture for both aerobic and anaerobic bacteria will be repeated during the study in case of new systemic infection suspicion

[v] Adverse events including SAEs will be collected from obtaining ICF through day 28; AEs that are not resolved should be followed-up until resolution or until determined as stable and due to known cause

[w] AEs of Day 0 are baseline AEs (not TEAE) starting after obtaining ICF until study drug administration

[x] Hospital length of stay (days), ICU stay (days), ICU free days, mechanical ventilation days/mechanical ventilation free days

[y] Screening SOFA: To include measurements of 6 organ system: cardiovascular, respiratory, renal, coagulation, GI/hepatic and CNS (To include evaluation of oxygenation either directly by arterial blood gas test or by calculation of PaO_2 from SpO_2, in case it is not possible to obtain arterial blood to determine the SOFA respiratory parameter)

Visit	1 Screening[a]	2 Day 1	3 Day 2	4 Day 3	5 Day 7 ±1 day	6 Day 10 ±1 day	7 Day 14 ±1 days	8 Day 21 ±1 days	9 Day 29 +3 days	10 3 months ±5 days
APACHE II Score[aa]	X									
Survival	→									
Hospital Readmissions									X	X[bb]

[z] Subsequent SOFA measurement (Days 1, 3, 7, and 14): taken once a day, in the morning adjusted to the time of normal routine assessment activities. To be calculated retrospectively. The following blood samples must be taken: CBC with platelet count, serum creatinine and bilirubin. In addition, clinical parameters should be evaluated and recorded (see Section **Error! Reference source not found.**)

[aa] For the required laboratory and clinical parameters (see Section **Error! Reference source not found.** of the protocol)

[bb] Capture data on any readmissions within 30 days of original hospital discharge

15 Appendix 6: Clinical Score Calculations

15.1 AKI Staging (KDIGO Criteria)

The following is provided in the Clinical Trial Protocol and is repeated here for convenience.

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥0.3 mg/dL increase	< 0.5 mL/kg/h for 6 h
2	2-2.9 times baseline	< 0.5 mL/kg/h for 12 h
3	3 times baseline OR Increase in serum creatinine to ≥4 mg/dL OR Initiation of renal replacement therapy	< 0.3 mL/kg/h for 24 h OR Anuria for ≥12 h

15.2 Twice the Serum Creatinine for Age, Race, and Gender

The following is provided in the Clinical Trial Protocol and is repeated here for convenience.

Age (years)	Black Males mg/dL (µmol/L)	Other Males mg/dL (µmol/L)	Black Females mg/dL (µmol/L)	Other Females mg/dL (µmol/L)
20 – 24	3.0 (266)	2.6 (230)	2.4 (212)	2.0 (166)
25 – 29	3.0 (266)	2.4 (212)	2.2 (194)	2.0 (166)
30 – 39	2.8 (248)	2.4 (212)	2.2 (194)	1.8 (160)
40 – 54	2.6 (230)	2.2 (194)	2.0 (176)	1.8 (160)
55 – 65	2.6 (230)	2.2 (194)	2.0 (176)	1.6 (142)
>65	2.4 (212)	2.0 (166)	1.8 (160)	1.6 (142)

15.3 SOFA – Sequential Organ Failure Assessment Score

The following is provided in the Clinical Trial Protocol and is repeated here for convenience.

Can range from 0-24.

Value	0	1	2	3	4
Respiratory PaO_2/FiO_2[1]	**>400**	**≤400**	**≤300**	**≤200 with respiratory support**	**≤100 with respiratory support**
Coagulation Platelets	**>150**	**≤150**	**≤100**	**≤50**	**≤20**
GI Total Bilirubin	**<1.2**	**1.2-1.9**	**2.0-5.9**	**6.0-11.9**	**≥12.0**
Cardiovascular[2]	**No hypo-tension**	**MAP <70**	**Dopa ≤5 PE <100**	**Dopa > 5 Epi ≤ 0.1 NE ≤ 0.1 PE 100-300**	**Dopa>15 Epi>0.1 NE>0.1 PE>300 VP>0.01**
Neurology GCS	**15**	**13-14**	**10-12**	**6-9**	**<6**
Serum Creatinine OR Urine Output	**<1.2**	**1.2-1.9**	**2.0-3.4**	**3.5-4.9 <500cc/ day**	**≥5.0 <200cc/ day**

1. For patients on supplemental oxygen via nasal cannula, nasopharyngeal catheter or mask and for converting SpO2 values to PaO2 use the attached oxygen conversion tables.
2. Doses of dopamine (Dopa), epinephrine (Epi), norepinephrine (NE) are in micrograms/kg/min; phenylephrine (PE) is micrograms/min; vasopressin (VP) is U/min. Vasopressors must have been administered for at least one hour.

16 Appendix 7: Prior and Concomitant Medications

16.1 Nephrotoxic Medications

- Acetaminophen
- Acetylsalicylic Acid
- Allopurinol
- Benazepriol
- Captopril
- Celecoxib
- Enalapril
- Esmoprazole
- Famotidine
- Furosemide
- Hydrochlorothiazide
- Ibuprofen
- Iodixanol
- Iohexol
- Iopamidol
- Irbesartan
- Ketorolac
- Lansoprazole
- Lisiopril
- Losartan
- Metolazone
- Omeprazole
- Pantoprazole
- Perflutren
- Ramipril
- Ranitidine
- Sodium Amiotrizoate
- Technetium (99 M) Mebrofenin
- Valsartan
- Zesoretic

16.2 Immunosuppresant Medications

- Corticosteroids
    - Prednisone >40 mg/day
    - Hydrocortisone 160 mg/day
    - Methylprednisolone >32 mg
    - Dexamethasone >6 mg
    - Cortisone >200 mg
    - Betamethasone >4.8 mg

- Methotrexate
- Leflunomide (Arava) / Teriflunomide (Aubagio)
- Cyclophosphamide (Cytoxan)
- Cyclosporine A
- FK506 (Tacrolimus)
- Azathioprine
- Mycophenolate Mofetil (MMF) (CellCept)
- Sirolimus (Rapamycin, Rapamune)
- Everolimus (Certican)
- Temsirolimus (Torisel)
- Gusperimus
- Thalidomide
- Antitumor Necrosis Factor (TNF) Agents
    - Entanercept (Enbrel)
    - Afelimomab (Fab 2)
    - Infliximab (Remicade)
    - Certolizumab (Cimzia)
    - Golimumab (Simponi)
- Interleukin-1 Receptor Antagonist (IL-1RA)
    - Kineret
- CTLA-4 Fusion Protein
    - Abatacept (Orencia)
    - Alefacept (Amevive)
    - Belatacept (Nulojix)
- Anti-CD20
    - Rituximab (Rituxan/MabThera)
    - Obintuzumab (Gazyva)
    - Ocrelizumab (Ocrevus)
    - Ofatumumab (Arzerra)
- Anti-CD52
    - Alemtuzumab (Campath)
- Anti-IL2

  - Daclizumab (Anti-Tac, Zenapax)
  - Basiliximab (Simulect)
- Anti-IL6
  - Tocilizumab (Actemra/RoActemra)
- Anti-BAFF (B-cell activating factor)
  - Belimumab
- Integrin Inhibitor
  - Natalizumab (Tysarbi)
- Anti-CTLA 4
  - Ipilimumab
- Other Interleukins
  - Aldesleukin (Proleukin)
  - Canakinumab (ilaris)
  - Oprelvekin (Neumega)
- Anti-PDL1
  - Avelumab (Bavencio)
- Other Selective Immunosuppressants
  - Muromonab or OKT-3
  - Efalizumab (Raptiva): Anti-CD11a
  - Fingolimod (Gilenya): Spingosine 1-phosphate receptor modulator
  - Eculizumab (Soliris): Anti-complement protein C5
  - Tofacitinib (Xeljanz): JAK-Stat Inhibitor
  - Apremilast (Otezla): PDE-4 Inhibitor
  - Vedolizumab (Entyvio): Integrin $\alpha 4\beta 7$

17 Appendix 8: CKD Definition and Classification

17.1 CKD Definition:

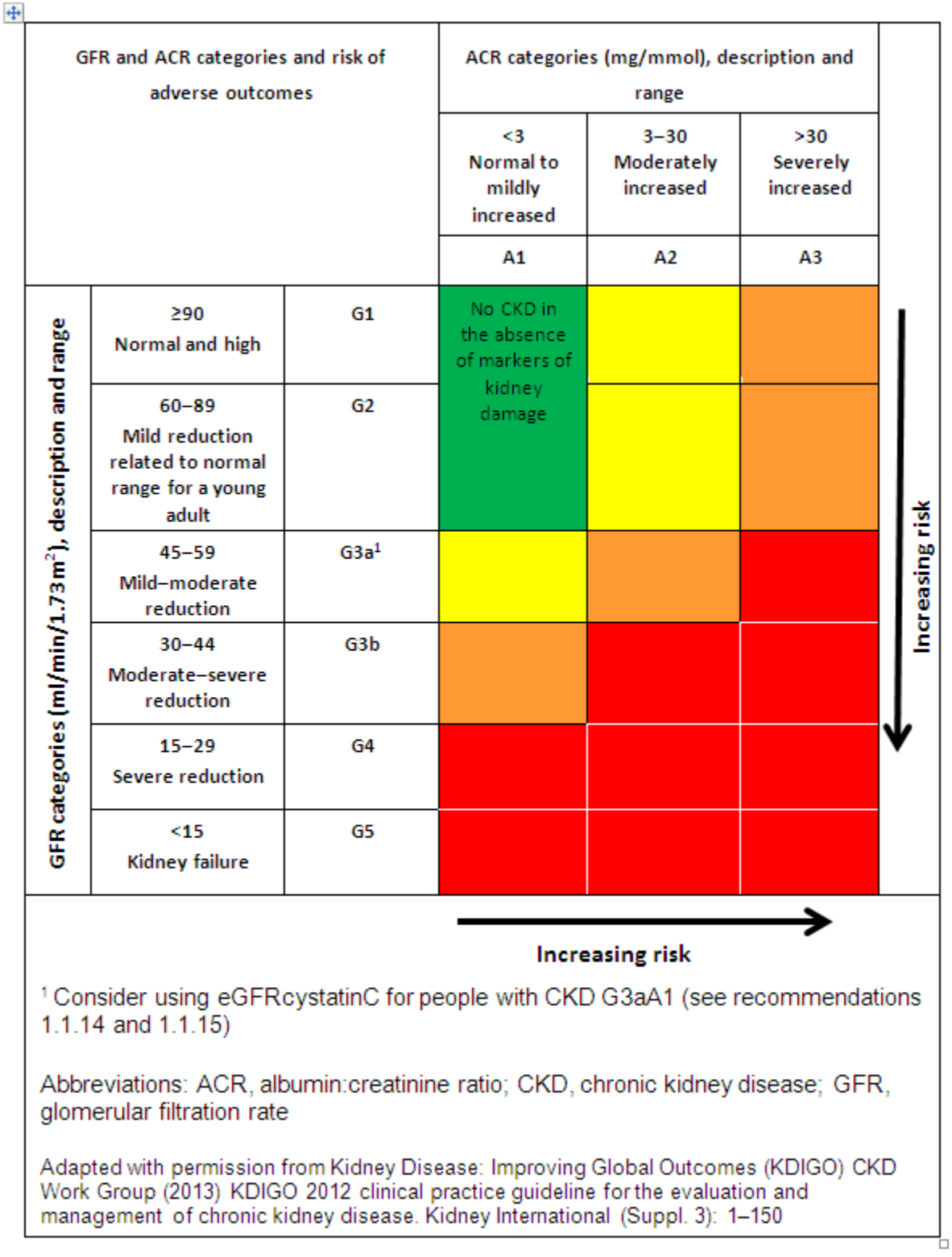
A patient is said to have chronic kidney disease (CKD) if they have abnormalities of kidney function or structure present for more than 3 months. The definition of CKD includes all individuals with markers of kidney damage (see below*) or those with an eGFR of less than 60 ml/min/1.73m2 on at least 2 occasions 90 days apart (with or without markers of kidney damage).

*Markers of kidney disease may include: albuminuria (ACR > 3 mg/mmol), haematuria (or presumed or confirmed renal origin), electrolyte abnormalities due to tubular disorders, renal histological abnormalities, structural abnormalities detected by imaging (e.g. polycystic kidneys, reflux nephropathy) or a history of kidney transplantation.

17.2 CKD Classification

CKD is classified based on the eGFR and the level of proteinuria and helps to risk stratify patients.Patients are classified as G1-G5, based on the eGFR, and A1-A3 based on the ACR (albumin:creatinine ratio) as detailed below:

Classification of chronic kidney disease using GFR and ACR categories



[1] Consider using eGFRcystatinC for people with CKD G3aA1 (see recommendations 1.1.14 and 1.1.15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150