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STATISTICAL ANALYSIS PLAN

Version 4.0

September 24, 2019

Product: Reltecimod

Protocol Number: ATB-202

Phase III, randomized, double-blind, placebo-controlled, parallel-group, study of Reltecimod as compared to placebo in patients with necrotizing soft tissue infections (NSTI)

Development Phase: Phase 3

IND Number: 67,785

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Statistical Analysis Plan
Version 4.0, 24 September 2019

"Phase III, randomized, double-blind, placebo-controlled, parallel-group, study of Reltecimod as compared to placebo in patients with necrotizing soft tissue infections (NSTI)"

SIGNATURE OF APPROVAL

Wayne M Dankner Date 24SEP2019

Wayne M Dankner, MD
Chief Medical Officer
Atox Bio, Ltd

Statistical Analysis Plan
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SIGNATURE OF APPROVAL

Greg Maislin Date 24 Sept 2019

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Table of Contents

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 provided in the Clinical Study Protocol and this SAP, the SAP prevails. This SAP will be finalized prior to unblinding of the treatment allocations 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 principals for clinical trials[1].

1.1 Revisions to SAP in Version 4.0

The prior version of this SAP was Version 3.0, September 14, 2015. The final updates included in this Version 4.0 of the SAP were made while treatment allocation remained blinded.

There are two primary types of updates. The first type of update relates to the secondary efficacy endpoints concerning AKI. The AKI endpoints are now harmonized with the AKI endpoints to be used in the currently enrolling AKI pivotal trial. The primary efficacy endpoint from the ongoing AKI trial (ATB-203) has now been specified formally as the **key secondary efficacy endpoint** for this trial to allow the results from this trial (ATB-202) to support those from the AKI trial.

This endpoint is freedom from durable loss of renal function defined as alive, free of dialysis, 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.

The second type of update generally relates to changes made to accommodate the needs of the NDA and future integrated summaries of safety and effectiveness in light of the observation that ATB-202 will form the bulk of the safety population for the NDA.

[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 efficacy hypothesis for this study concerns superiority of Reltecimod relative to placebo and may be symbolically represented as follows:

Ho: $\pi_{0.50} - \pi_{Placebo} = 0$ vs Ha: $\pi_{0.50} - \pi_{Placebo} > 0$;

where $\pi_{0.50}$ and $\pi_{Placebo}$ represent the true probability that a patient achieves a specific composite clinical success criteria, NICCE (Necrotizing Infections Clinical Composite Endpoint), designed to be sensitive to both local and systemic drug effects. Each probability represents the proportion of subjects on each arm expected to respond according to NICCE. A validation study of the NICCE endpoint has recently published (Bulger et al 2017[2]).

2.1.2 Primary Efficacy Endpoint

To be considered a success in terms of the primary endpoint, each patient must meet all components of NICCE as summarized in the following table.

Component	**NICCE**
Survival	• Alive at Day 28
Local component	• ≤3 debridements through Day 14 • No amputation beyond first debridement*
Systemic component	• mSOFA score of ≤1 at Day 14 • Reduction of ≥3 score points between baseline and Day 14 mSOFA score

*Amputation is defined as removal of a limb or portion of a limb to the level of a joint space

An unadjusted chi-square test using a two-sided type 1 error of α=0.01 will be used to test superiority of Reltecimod relative to placebo for the primary endpoint (NICCE). Primary results will include the numbers and percentages of patients achieving NICCE in each treatment group, the p-value from the chi-square statistic, as well as the estimated treatment group difference in NICCE success rates with 99% confidence interval.

2.1.3 Conditional Co-Primary Efficacy Endpoint

The following modified clinical composite endpoint will be evaluated as the conditional co-primary endpoint (CCPE). The CCPE removes the systemic component of composite endpoint. Analysis of the CCPE was added at the request of FDA.

[2] Bulger EM, May A, Dankner W, Maislin G, Robinson B, Shirvan A. Validation of a clinical trial composite endpoint for patients with necrotizing soft tissue infections. J Trauma Acute Care Surg. 2017 Oct;83(4):622-627. doi: 10.1097.

Component	CCPE
Survival	• Alive at Day 28
Local component	• ≤3 debridements through Day 14 • No amputation beyond first debridement*

*Amputation is defined as removal of a limb or portion of a limb to the level of a joint space

Patients must meet all three of the above components in order to be considered a success for the CCPE.

A two-sided unadjusted chi-square test will be used to test superiority of Reltecimod relative to placebo in terms of the CCPE. The type 1 error rate for testing superiority in terms of the CCPE will be set to α=0.05. Results for the CCPE will include the numbers and percentages of patients achieving CCPE in each treatment group, the p-value from the chi-square statistic, as well as the estimated treatment group difference in CCPE success rates along with a 95% confidence interval.

2.2 Overall Study Success Criterion

The overall Study Success criterion, agreed upon with FDA, is to simultaneously observe $p \leq 0.01$ for the NICCE endpoint and $p \leq 0.05$ for the CCPE.

2.3 Key Secondary AKI Endpoint

The same endpoint that is being currently employed in the ongoing ATB-203 study of AKI in sepsis will be evaluated as the key secondary endpoint in this study. The key secondary endpoint is ***freedom from durable loss of renal function at Day 28***. Only subjects with AKI Stage 2 or Stage 3 prior to initial drug dosing will be included in this comparison. The key secondary 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 Day 14 and 28 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. A sensitivity analysis will utilize an independently adjudicated reference value to determine baseline eGFR.

To control type 1 error for the key secondary efficacy endpoint, superiority of Reltecimod relative to placebo in terms of freedom from durable loss of renal function at Day 28 among those presenting with Stage 2 or Stage 3 AKI will only be interpreted as a confirmatory hypothesis test if $p \leq 0.01$ for the primary endpoint (NICCE) and $p \leq 0.05$ for the co-primary endpoint (CCPE).

Otherwise, treatment group comparisons in terms of the key secondary efficacy (AKI) endpoint will be interpreted as a descriptive endpoint. An unadjusted chi-square test using a two-sided type 1 error of α=0.05 will be used to test superiority of Reltecimod relative to placebo for the key secondary AKI endpoint.

2.4 Sample Size Justification

2.4.1 Primary Endpoint

This trial will enroll 290 subjects that will be randomized in a ratio of 1:1 to either Reltecimod 0.50 mg/kg (n=145) or placebo (n=145), each in addition to standard of care. Sample size analysis was performed assuming that all patients will be evaluable for the primary endpoint. This assumption is justified on the basis of results from the Phase 2a trial and the Retrospective Study in which all patients were evaluable in terms of the definitions used to construct the NICCE endpoint.

The primary efficacy hypothesis will be tested using an unadjusted χ^2 statistic with an α=0.01 two-sided significance level. Statistical power was computed for a range of expected treatment group differences supported by the results of the preliminary studies noted above. For expected treatment group differences of 0.30, 0.25, and 0.20, statistical power will be 99%, 95.9%, and 80.2%, respectively. These power determinations were conservatively made assuming an average success rate between treatment groups of 0.5. In this way power estimates are applicable across the range of expected response rates; but may be conservative in some cases.

The use of NICCE and this range of expected treatment effects is supported by preliminary studies as summarized in the following table.

	Percentage Achieving NICCE	(n/N)
Phase 2a (mSOFA≥3) Reltecimod 0.50 mg/kg	71.4%	(5/7)
Phase 2a (mSOFA≥3) Placebo	20.0%	(1/5)
Retrospective Study (mSOFA≥3)	30.4%	(21/69)

In the Phase 2a trial, 71.4% (5/7) patients with baseline mSOFA≥3 treated with Reltecimod (at a dose of 0.50 mg/kg) achieved NICCE. In contrast, only 20% (1/5) of placebo patients with baseline mSOFA≥3 achieved NICCE, a difference of 51.4%. The Retrospective Study provides further support for the untreated response rate. Among 69 patients with baseline mSOFA≥3, 30.4% (21/69) achieved NICCE, a difference of 41.0% relative to Phase 2a patients in the 0.50 mg/kg treated group presenting with screening mSOFA≥3.

Given the selected sample sizes, if the observed differences in this study happen to be equal to 35%, 25%, or 20% (centered about 50%), then the corresponding 2-sided p-values will be

p<0.0001, p<0.0001, and p=0.0007, respectively. The observed difference will need to be larger than about 16% (e.g., 58% vs 42%) for p≤0.01 (again assuming that the average success rate between groups is 50%).

2.4.2 Conditional Co-Primary Endpoint

Statistical significance for the co-primary endpoint will be evaluated using a two-sided type 1 error rate of α=0.05. The conditional co-primary endpoint (CCPE) will only be formally tested for superiority if the primary NICCE endpoint demonstrates Reltecimod superiority at p≤0.01.

Based on a similar evaluation of the preliminary studies discussed above, this study was designed to have very large statistical power for the conditional co-primary endpoint when the true expected CCPE success rates are 80% and 60% (difference of 20%) in the Reltecimod 0.5 mg/kg and placebo treatment groups, respectively. Under these assumptions power is 96.4%. However, if the true rates are 78% vs 62% (difference of only 16%), then power remains relatively high at 84.8%. The total sample size has also been selected to obtain sufficient enrollment on the treatment arm for relevant secondary effectiveness endpoints and for safety endpoints.

2.5 Randomization

290 patients will be recruited into the study and randomized to either Reltecimod 0.50 mg/kg or placebo in a 1:1 ratio. Randomization will be within site stratified by presence (+) of a diagnosis of Fournier's Gangrene versus absence (-) and whether the screening mSOFA score is >4 (+) or 3-4 (-) (See Tables 14.1.1.1 to 14.1.1.4). In the Retrospective Study analysis set with screening mSOFA ≥ 3 (N=69), the median mSOFA value was 4 and 46.6% had values >4. Thus, the stratification for mSOFA is expected to roughly reflect a median split.

Four computer generated, blocked randomization lists will be provided for each site corresponding to the cross-tabulation of Fournier's Gangrene (+ vs -) and baseline mSOFA >4 (+ vs -) category status. Within each block, half of the assignments will be to active drug and half to placebo, in random order. Block sizes will be randomly varied as an additional masking feature.

The following will be done to insure balance through randomization. Every initial randomization code will end in '-1'. If a randomization code is used but the patient does not receive drug due to lack of confirmatory surgical NSTI diagnosis[3], then the randomization code is not reused. Instead, the next patient from same stratum, (+,+), (+,-), (-,+), or (-,-) as the non-dosed patient, will receive the same allocation and the same randomization code except that the new code will end in '-2' while the old code ended in '-1'. In this way, randomization codes are not re-assigned which can cause confusion but the same drug allocation using the digits prior to the '-' are used, thereby preserving balance.

2.6 Analysis Sets

The following analysis sets are defined:

[3] It is an unavoidable medical fact that NSTI diagnosis requires surgical confirmation and that randomization may occur prior to surgical confirmation in order for the treatment to begin at the optimal time frame. This presents the need to add a design feature that maintains within stratum balance; yet avoids the operational need for never applying the exact same randomization ID to more than one patient.

- Intent-to-treat (**ITT**): The **ITT (Randomized) Set** is defined as all randomized patients according to the intended study treatment.

- As-Treated (**AT**): The AT analysis set will include the subset of ITT patients who were exposed to study medication (active or placebo) and categorized according to the treatment actually received. This analysis set will be often referred to as the **As Treated (Safety) Analysis Set**.

- 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 NSTI based on surgical verification. **The mITT analysis set will be used in primary effectiveness analyses with patients assigned to their intended randomized**.

- Per Protocol (**PP**): Optionally, a PP analysis set may be used in secondary effectiveness analyses. The PP analysis set would include patients in the mITT analysis set assigned according to actual treatment received rather than intended treatment; and excluding patients with one of the following:

  1. Significant violations of inclusion or exclusion criteria with a reasonably important potential to confound estimates of drug effects,

  2. Post randomization protocol violations with potential to confound estimates of treatment effects, or

  3. Patient death within 1 day of dosing.

Exclusions from the PP analysis set will be determined based on blinded clinical data. If a PP analysis set is defined, analyses will be limited to the subset of tables listed in Section 3.2 to be used in pre-planned exploratory sub group stratified analyses.

2.7 Futility analyses

A futility analysis will be performed based on the results of the first 100 patients (50 per group). The futility decision will be based on the predictive probability of eventual study success, conditioned on the data available at interim analysis. Independent, non-informative Bayesian prior distributions are assumed for the expected NICCE success rates for both treatment groups, namely, $\pi_{0.50} \sim$ Beta(1,1), $\pi_{Placebo} \sim$ Beta(1,1) for the active and placebo groups, respectively.

The Bayesian predictive probability of being able to demonstrate superiority of Reltecimod relative to placebo at a two-sided α=0.01 when the remaining patients are finally observed will be determined. The trial will stop enrollment for futility if this predictive probability is below a lower bound threshold of 10%.

The following table summarizes what the observed predictive probabilities will be as a function of magnitude of the treatment group difference and assuming an observed control success rate of 0.40. For example, if there are 20 success and 30 failures among placebo controls (40% success rate) at the interim analysis, then the futility boundary will be crossed if the number of active successes is 22 (44%) or less, that is, if the observed treatment group difference is 4% or less.

Diff	0.000	0.020	0.040	0.060	0.080	0.100	0.120	0.140	0.160	0.180	0.200	0.220	0.240	0.260	0.280	0.300
PP	0.029	0.050	0.082	0.127	0.187	0.261	0.348	0.444	0.543	0.639	0.728	0.804	0.866	0.913	0.946	0.969

The futility bound is 'non-binding' in the sense that no effort was made to 'recover' alpha to increase power.

2.8 Control of blinding and DMC

2.8.1 Randomization and Unblinded Study Statistician

There are three statisticians in this study with different roles:

Blinded primary study statistician – primary lead statistician

Unblinded study statistician – performs randomization and provided back-up

Unblinded DMC statistician independent statistician supporting DMC operations

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 DMC statistician,

Serve as a backup unblinded statistician.

In advance of study initiation, programming for the blocked randomized treatment allocation with randomized block size was developed. The program to perform this randomization was written in SAS with a Proc IML call to R and is provided in Appendix 6.

A preliminary randomization 'test' seed was used to generate a set of preliminary randomization ID numbers. These were exported to site-specific Excel files and also summarized in a single SAS listing report (RTF format). The unblinded study statistician will use this program to determine final (blinded) randomized allocations and will provide these to the contract drug dispenser in an agreed upon format. A variable indicating the blinded treatment allocations will not be part of the clinical study data to be managed by the data management CRO. This is to eliminate any 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.

2.8.2 Data Monitoring Committee and Unblinded DMC Statistician

A Data Monitoring Committee (DMC) will be utilized in this study which will be reviewing safety outcomes at a prescribed regularity in addition to helping to facilitate the unblinded futility analysis. The Charter will provide decision rules, composition of the DMC members and their conflict of interest statements. This DMC will include an ***unblinded DMC statistician***.

Analysis staff under the direction of the primary study statistician will develop SAS based programs that process clinical data provided by the blinded data management CRO to populate planned safety analysis tables and listings, but in a blinded fashion. This includes using a pseudo randomization for purposes of table generation program development. This programming and relevant data will be provided to the independent unblinded DMC statistician.

As mentioned above the ***unblinded study statistician*** has limited roles for this study. This individual will perform the final randomized allocation and will provide the unblinding codes to

the unblinded DMC statistician who will run programs to populate selected tables in an unblinded fashion. If needed, the unblinded study statistician may work with the unblinded DMC statistician to resolve difficulties and can serve as a backup unblinded statistician if needed.

The independent unblinded DMC statistician will perform the necessary computations involving the Bayesian predictive power to be used in the planned futility assessment at the planned interim analysis based on the results from the first 100 evaluable patients.

3 Description of Variables to be Included in Statistical Analyses

3.1 Medical and Surgical History

Details of the NSTI will be recorded on the case report form (CRF) and include: "clinical diagnosis" (as a specific subset of NSTI) at the time of enrollment; location of primary infection; date of onset, identified predisposing factors (trauma, surgery, IV drug use, and co-morbidities such as diabetes or vascular insufficiency; prior surgical procedures related to the etiology of the NSTI; prior surgical procedures for the treatment of the primary infection site; antimicrobial use from the date of onset of current illness if available [may predate diagnosis of NSTI]). A medical history identifying active medical or surgical conditions will be reported on the CRF. All chronic medications will be identified and characterized by dose and frequency as well as reason for use.

3.2 Physical Examinations

Physical exam will include both the primary site of the necrotizing soft tissue infection and a clinically appropriate examination of vital organ systems. These include cardiovascular, respiratory, abdomen, extremities, neurologic body systems, and other.

3.3 Concomitant Medication

All concomitant medications antimicrobial & non-antimicrobial will be entered into the CRF and identified by their generic or trade name. Information will include the dose, dosing frequency, route of administration, duration (start and stop dates), and reason for administration. Concomitant medications will be collected up through Day 28.

3.4 Vital Signs

Vital signs include weight, heart rate, systolic and diastolic blood pressure, mean arterial blood pressure (MAP) respiratory rate (spontaneous or controlled) and temperature. While these may be determined many times during the course of the patient hospitalization, recording vital signs in the CRF will be based on once daily readings for specified time sequences according to the time and events schedule.

3.5 Clinical Scores

Clinical scores/criteria components will be collected in the study. APACHE II and LRINEC scores along with Anaya criteria are obtained only at screening while SOFA score is obtained throughout the study. Computational details for all scores are presented in the Appendix 5.

3.5.1 Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score

The LRINEC score (Wong, Khin et al. 2004)[4] is only obtained at screening and will be used to described baseline disease severity. LRINEC ≥ median vs LRINEC < median will be used in the exploratory stratified analyses.

[4] Wong CH, Khin LW, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004: 32(7): 1535-1541

3.5.2 ANAYA criteria

The ANAYA criteria (Anaya, Bulger et al. 2009) are only obtained at screening and will be used to described baseline severity. ANAYA ≥ median vs ANAYA < median will be used in the exploratory stratified analyses.

3.5.3 Acute Physiology and Chronic health Evaluation II (APACHE II) score

APACHE II scores are another measure of disease severity to be obtained at screening. APACHE II ≥ 10 vs APACHE < 10 will be used in the exploratory stratified analyses.

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. If this is the case then the APACHE II scores will not be considered part of the audited clinical data set provided by the data management CRO.

3.5.4 Sequential Organ Failure Assessment (SOFA) Score

A modified version of the SOFA score will be used as a clinical end point and will be calculated as described in Section 5.2 and Appendix 5. The modification is that the liver component is not used. Individual parameters of the SOFA score will be collected as summarized as well as the modified SOFA total score (mSOFA). Data will be recorded in the CRF at specified time points according to the time and events schedule. Additionally, SOFA will be computed and described for screening, Day 7, and Day 14. Additional handling of the neuro deficit component is described below.

3.6 Electrocardiogram

12-lead electrocardiogram will be according to time and events schedule. The following parameters will be recorded for each ECG: PR interval, RR interval, QRS complex time, QT interval and Corrected QT interval (QTc). Additionally, descriptive text will be provided for any ECG abnormalities as evaluated by site personnel.

The primary ECG results will be obtained from an independent and blinded cardiology central reader including QTcB and QTcF as well as the measures listed above.

3.7 Clinical Laboratory Assessments

Safety laboratory assessments will be performed according to the to the time and events schedule (See Clinical Study Protocol).

3.8 Microbiology

Microbiological testing will be performed as described in the Clinical Study Protocol and time and events schedule.

3.9 Use of additional concomitant therapy

The following measures of additional medical therapies will be recorded:

- Hyperbaric oxygen
- Intravenous gamma globulin (IVIG)
- Plasmapheresis

4 Secondary and Exploratory Endpoints

4.1 AKI Related Endpoints

4.1.1 Freedom from Durable Loss of Renal Function at Day 28

The same endpoint that is being currently employed in the ongoing ATB-203 study of AKI in sepsis will be the key secondary endpoint in this study. Only subjects with AKI Stage 2 or Stage 3 prior to drug dosing will be included in this comparison.

The key secondary AKI endpoint is ***freedom from durable loss of renal function at Day 28*** defined as alive, free of dialysis, 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 at Day 14 and 28 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. A sensitivity analysis will utilize an independently adjudicated reference value to determine baseline eGFR.

To control type 1 error for the key secondary efficacy endpoint, superiority of Reltecimod relative to placebo in terms of freedom from durable loss of renal function among those with Stage 2 or Stage 3 AKI prior to dosing, will only be interpreted as a confirmatory hypothesis test if $p \leq 0.01$ for the primary endpoint (NICCE) and $p \leq 0.05$ for the co-primary endpoint (CPEP). Otherwise, treatment group comparisons in terms of the key secondary efficacy (AKI) endpoint will be interpreted as a descriptive endpoint. An unadjusted chi-square test using a two-sided type 1 error of $\alpha=0.05$ will be used to test superiority of Reltecimod relative to placebo for the key secondary AKI endpoint.

4.1.2 Blinded Independently Adjudicated AKI Endpoints and Analyses

Reference creatinine values, maximal AKI stage, and AKD stage at Day 14 will be determined by a blinded independent adjudication committee as described in the Clinical Study Protocol. AKI Stage assigned through blinded independent adjudication will be for Maximal stage by KDIGO criteria using creatinine and/or urine output over the first 7 days post screening. For these analyses, subjects with a maximal AKI Stage 2 or AKI Stage 3 will be included. Descriptive comparisons will be made between the Screening (pre-dose) AKI stage and Maximal AKI stage and between the Day 14 algorithmically determined endpoints to the Day 14 independently adjudicated endpoint.

4.1.3 Other AKI Endpoints

Exploratory AKI endpoints include the primary endpoint evaluated at Day 14, improvement in durable loss of renal function defined as alive, free of dialysis and improvement leading to a lower AKI stage but no better than Stage 1 AKI evaluated at Day 14 and Day 28, and AKD stage evaluated at Day 14 and Day 28.

4.1.4 Algorithmic Determinations

4.1.4.1 Reference

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.

Exhibit 1. Algorithmic Determination of Reference Creatinine

Pre processing 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[5,6] 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;
```

[5] 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.

[6] 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]

```
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)  ;
      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;
```

4.1.4.2 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.

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).

As a sensitivity analysis, when determining AKI endpoints, the adjudicated reference creatinine will be used in place of the algorithmically determined reference value.

4.1.4.3 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.

4.1.4.4 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.

4.1.4.5 Determining AKD Stage at Day 28

Exhibit 2 will also be used to determine AKD Stage at Day 28 except that the criterion for renal replacement therapy is an ongoing need rather than initiation.

4.1.4.6 Determining AKD Stage at Day 14

Similarly, Exhibit 2 will be used to determine AKD Stage at Day 14 except that the criterion for renal replacement therapy is an ongoing need rather than initiation.

4.1.4.7 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 14-28 day range as the recovery creatinine.

4.1.5 Processing of Adjudicated AKI Data

Three independent adjudicators will determine:

- Reference Creatinine
- Maximal AKI Stage (over first seven days)
- AKD Stage at Day 14

The adjudicated reference will be the mean of the three adjudicated values.

The adjudicated Maximal AKI Stage and AKD Stage at Day 14 will be determined through 'vote counting'.

Independent adjudication of AKD stage will be used to determining ***Achieving Freedom from Durable Loss of Renal Function at Day 14*** and ***Improvement in Durable Loss of Renal Function at Day 14*** in sensitivity analyses.

4.2 Primary Endpoint Components and Other mSOFA Related Outcomes

The primary endpoint components and other mSOFA related outcomes will be evaluated as additional secondary efficacy endpoints in descriptive treatment group comparisons using the statistical methods summarized below.

- Distribution of mSOFA scores at Day 14
- Kaplan-Meier analysis of the time to resolution of mSOFA score to ≤ 1 with censoring at Day 14
- Kaplan-Meier analysis of the time to resolution of mSOFA score to ≤ 1 up to Day 28
- Single components of the primary composite end point:
    - Alive at Day 28
    - Debridements by Day 14 ≤3
    - Number of amputations (removal of a limb or portion of a limb to the level of a joint space) (done after first debridement)
    - mSOFA score on Day 14 ≤1
    - Reduction of ≥3 score points between baseline and Day 14 mSOFA score.

- Clinical local parameters:
    - Number of debridements to days 7, 10, and 14 Proportion of patients needing (up to Day 14):
        - only one debridement to control the infection
        - 2 debridements to control the infection
        - 3 debridements to control the infection
        - ≥3 debridements to control the infection
        - >3 debridements to control the infection

- Clinical systemic parameters:
    - Evaluation of organ function over time, using mSOFA score (total score and organ specific score)

4.3 Critical care and hospital stay parameters

The following critical care and hospital stay parameters will be measured up to Day 28. These parameters relate to medical and procedures costs:

- ICU free days
- Days in ICU
- Days on ventilator
- Ventilator free days
- Vasopressors days/ Vasopressors free days
- Hospital length of stay (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[7]). 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 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 a 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/vasopressor 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.

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

The table summarizing critical care related outcomes will also be presented stratified according to the set of baseline covariate stratified analyses defined below. In addition, critical care related outcomes will be similarly summarized and compared between patients with NICCE success and NICCE failure.

4.4 C - Reactive Protein (CRP)

CRP will be summarized for measurements made at Screening, Day 14, and for changes from Screening to Day 14. CRP is not considered a safety endpoint. Therefore, CRP will be summarized in the mITT Analysis Set .

4.5 Exploratory Endpoints

The following will be assessed as exploratory endpoint.

- Distribution of observed mSOFA at Days 21 and 28.

4.6 Exploratory Subgroup Analysis

Exploratory subgroup analysis will be performed. For these exploratory analyses, primary efficacy, selected secondary efficacy, selected safety tables will be repeated stratified according to the following classifications:

1. Age ≥ 65 years vs. < 65 years
2. Gender
3. BMI (<30 versus 30-<40 vs. ≥ 40 kg/m^2),
4. White vs. non-white
5. AKI Status (Any AKI, Stage 2/3 AKI, non-AKI).
6. Patients Achieving Freedom from Durable Loss of Renal Function vs. not (among patients presenting with Stage 2 or Stage 3 AKI)
7. Presence of cardiovascular organ failure (SOFA component >=3 at baseline) vs. those without CV organ failure (except SOFA related tables)
8. Presence of respiratory organ failure (SOFA component >=3) at baseline vs. those without (except SOFA related tables)
9. LRINEC ≥ median vs. LRINEC < median
10. ANAYA ≥ median vs. ANAYA < median
11. APACHE II ≥ 10 vs. APACHE <10
12. Type of bacteria (Gram-positive vs. Gram-negative and possibly a ‘mixed’ type if needed), list to be provided by Sponsor and other prevalent pathogens.
13. Prevalent sub types and classes of identified pathogens
14. Bacteremic vs. non-bacteremic (blood culture)

The results for any subgroup analysis will not be interpreted if there are fewer than five patients in either treatment group within that subgroup analysis.

The following tables will be provided for stratifications 1 through 11 listed above. These tables are described in more detail below. Only the primary endpoint table (Table 14.2.1.1) will be stratified for the subgroups 12, 13, and 14.

14.2.1.1	Comparisons of the Percentages of Patients Achieving Primary Composite Clinical Success Endpoint (NICCE) and its Components mITT Analysis Set†
14.2.1.2	Comparisons of the Percentages of Patients Achieving Conditional Co-Primary Endpoint (CCPE) and its Components mITT Analysis Set†
14.2.2.2	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 14 Last Observation Carried Forward (LOCF) mITT Analysis Set†
14.2.2.4	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 14 Change from Day 0 (Screening) - Last Observation Carried Forward (LOCF) mITT Analysis Set†
14.2.2.6	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 14 Change from Day 1 - Last Observation Carried Forward (LOCF) mITT Analysis Set†
14.2.4.1	Critical Care and Hospital Stay Parameters Over Days 1 to 28 By Treatment Group mITT Analysis Set†
14.2.5.1	Cumulative Number of Debridements to Days 7, 10, and 14 By Treatment Group mITT Analysis Set†
14.2.5.2	Percentage of Patients Requiring 1, 2, 3, >=3, and >3 Debridements Through Day 14 By Treatment Group mITT Analysis Set†
14.2.6.2.1	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 28 Algorithmic Determination of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 28 Status Using LOCF& Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Algorithmic Reference
14.3.1.1	Summary of Treatment-Emergent Adverse Events (TEAEs) Overall and by Treatment Group As Treated (Safety) Analysis Set†

4.7 Microbiology

By-Pathogen and By-Patient bacteriological responses will be summarized as follows:

- *By-Pathogen Bacteriological Response:* The by-pathogen bacteriological response for each causative organism identified at baseline (BL) will be defined as follows:
  - Eradication: BL causative organism cannot be isolated from any culture(s) obtained from a debridement performed on or after study Day 3.
  - Persistence: The BL causative pathogen is isolated from a debridement performed on or after study Day 3.

- *By-Patient Bacteriological Response:* The by-patient bacteriological response will be determined according to the following definitions:
  - Eradication: All BL causative organism(s) have a response of Eradication.
  - Persistence: All or some BL causative organism(s) have a response of Persistence.

Presence of pathogens will be determined using blood and tissue cultures. Treatment group comparisons of response rates will only be performed if there at least 5 instances of a unique pathogen in both groups and are limited to patients with microbiological samples at screening and at follow-up (i.e., day 3). By-patient microbial responses will be based on worst response.

Pathogens will also be categorized into Gram-positive / Gram-negative and into aerobic and anaerobic sub types.

Prevalent sub types and classes of identified pathogens will be used in sub group analyses of clinical response as described above.

5 Analysis Approaches

5.1 Baseline Comparisons

Demographic and baseline characteristics will be summarized for each analysis set overall and by treatment group. Categorical variables including race, ethnicity, and gender will be summarized by counts and percentages. Continuous variables will be summarized using mean, median, standard deviation (SD), and minimum and maximum values. Continuous variables evaluated will include age, BMI, height, weight, systolic BP, diastolic BP, MAP, heart rate, and temperature; as well as ANAYA, LRINEC, and APACHE II scores. Presence of baseline sepsis will be summarized according to the numbers and percentages of patients with baseline cardiovascular and respiratory organ failure as reflected in screening component SOFA scores of 3 or 4. In addition presence of any AKI at baseline algorithmically determined, Stage 2/3 AKI at screening, and maximal AKI Stage 2/3 as assigned by the blinded adjudication panel will be summarized.

Analyses will be performed to confirm that the randomization resulted in no clinically significant group differences at baseline. 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. If there are clinically important baseline differences, multiple logistic regression will be used in supporting analyses to assess the impact of the imbalance on significance levels.

5.2 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)[8],[9]. Each of six organ systems are evaluated (see Appendix 5) with ordinal scores 0 to 4. A total score is the sum of the component scores. For this study, the liver component is excluded 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.

mSOFA scores will be assessed as 1) observed cases, 2) last observation carried forward (LOCF), 3) using MMRM, and 4) categorized and combined with mortality and local activity as part of the primary composite clinical success endpoint, NICCE.

The following will be defined as OBSERVED mSOFA.

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

[8] 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.

[9] 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.

2. If two or more individual organ scores are missing for mSOFA on Day 14 or earlier, but at least one individual organ score is non-missing, the individual organ scores will be imputed using last observation carried forward. In this case, it is possible that different components come from different visits. This will not be done at Day 21 and Day 28.

The following will defined mSOFA LOCF.

3. If all organ scores are missing on Day 14 or earlier, the mSOFA total score from that day will be imputed using last observation carried forward with the following exception.
    a. LOCF will not be performed after patient death.
    b. Note that LOCF will not be performed for unavailable mSOFA total scores at Day 21 and Day 28.
4. When summarizing the individual organ scores apart from the mSOFA total scores, the same rules as above will apply.
5. Patients with recorded screening mSOFA inflated by GCS scores due to mechanical ventilation or due medications will have their GCS score removed when determining screening mSOFA. This is to prevent subjects meeting trial inclusion just on the basis of GCS.

Since LOCF will not be applied to missing mSOFA scores after patient death in analyses that employ LOCF to describe mean values of time, there may be some 'diminishing n' and focus is therefore on morbidity rather than mortality.

5.2.1 Mean and Mean Changes Over Time

Mean values (SD) for the mSOFA and for the 5 specific organ components will be summarized over time with and without last-observation-carried-forward (LOCF). Similarly, mean (SD) changes scores from both day 0 and day 1 will be summarized with and without LOCF.

5.2.2 mSOFA as Part of Primary Endpoint

The primary efficacy endpoint (NICCE) employs mSOFA in two of its five components. NICCE success requires mSOFA at Day 14 ≤ 1 and the improvement from screening Day 0 to Day 14 that is ≥ 3.

5.2.3 Time to Organ Dysfunction Resolution

Time to organ dysfunction resolution will be evaluated as a time-to-event endpoint. This will be assessed in descriptive analyses using survival and life-table methods[10] and calculated from time of drug administration. Organ dysfunction resolution will be defined as mSOFA score ≤ 1. Two analyses will be performed. The first corresponds to the primary efficacy endpoint and evaluates time to mSOFA score ≤ 1 censoring at Day 14. The second extends the follow-up range to Day 28 using available observed mSOFA.

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

5.2.4 Mixed Models for Repeated Measures (MMRM)

Supporting longitudinal analyses comparing mSOFA means and mean changes over time will be implemented using mixed models for repeated measures (MMRM). The analysis set for the MMRM will not include LOCF imputation. Methods for this approach are described below.

5.3 Assessment of poolability among sites

Site poolability for the primary and co-primary endpoints will be evaluated using a random effects meta-analysis approach using the R package ***metafor*** to implement the analysis[11]. True effects will be evaluated on the logit scale and 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 [12]. I^2 is the fraction of $\boldsymbol{\tau^2}$ that is due to effect size heterogeneity (among sites), as opposed to sampling variance (within site). Fractions 25% and less are considered small (see references). 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 NICCE is the same for treated and placebo patients accounting for site-to-site heterogeneity in treatment effects.

5.4 Analyses Accounting for Stratification Factors

As noted above, randomization will be within site stratified by presence (+) of a diagnosis of Fournier's Gangrene versus absence (-) and whether the screening mSOFA score is >4 (+) or 3-4 (-). An unadjusted chi-square test using a two-sided type 1 error of α=0.01 will be used to test superiority of Reltecimod relative to placebo for the primary endpoint (NICCE). The corresponding 99% confidence interval will be determined.

Analyses will be performed to evaluate the potential impact of the stratification factors (presence versus absence of Fournier's gangrene and screening mSOFA equal to 3-4 versus >4). The estimated overall treatment group difference controlling for these two stratification factors, the stratum adjusted significance level for testing the superiority hypothesis, and the corresponding 95% confidence interval for the group difference in Month 24 CCS will be determined using a generalized linear model. The model covariates are treatment group and a categorical variable (df=3) for randomization stratum. The model parameters will be estimated using SAS Proc Genmod with distribution set to ***binomial*** and link set to ***logit***. The stratum adjusted success rates and standard errors of the success rates are determined on the probability scale using the ***ilink*** option in a ***lsmeans*** statement with a ***diff*** option. This statement produces a stratum adjusted significance level. The standard error on the probability scale for the difference in NICCE success rates needed for the 99% confidence interval will be determined as the square root of the sum of the device group specific standard errors which are generated as part of model estimation. The significance level for the stratum by treatment group difference interaction will be reported from a model in which the interaction is added. Within stratum differences and 95% confidence intervals will be summarized in descriptive analyses.

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[11] Viechtbauer W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. J Educ Behav Stat. 2005;30(3):261-293.

[12] Higgins JP, Thompson SG, Deeks JJ. Altman DG. Measuring inconsistency in meta-analyses. BMJ: 327(7414):557

The goal of the stratified randomization is to promote good balance of the stratification factors within site between the two treatment groups. It is possible that subjects will be assigned to a randomization stratum in error. If there are any subjects that are assigned to the incorrect stratum, then these analyses will be repeated using the subjects' true stratification status. To this end, significance levels and relative success rates with confidence intervals will be determined and compared for the primary and conditional co-primary endpoints for three scenarios. These three scenarios are:

1) Not accounting for stratified randomization (primary),

2) control for the actual stratification using a generalized linear model, and

3) control for strata defined based on actual subject status using a generalized linear model.

For example, if a subject was identified with a diagnosis of Fournier's Gangrene but it is later discovered that the subject actually did not actually have Fournier's Gangrene, then this subject would be moved into the correct stratum in scenario 3. In addition to the overall summary measures across strata, results within strata for scenarios 2 and 3 will be summarized.

5.5 Analysis of other covariate effects

Covariates may be assessed for potential confounding (due to imperfect randomization balance) or effect modification (subgroup efficacy heterogeneity) using multiple logistic regression. Covariates to be considered will include age, race, sex, site, and severity scores at baseline (i.e., APACHE II, Anaya[13] and LRINEC[14]). Other baseline variables in which randomization failed to produce adequate balance between groups (if any) will be examined in supporting analyses. This will be done through stratified analyses or multiple logistic regression. Covariate effects on estimates and interactions with treatment effects will be assessed as needed to evaluate treatment effect heterogeneity. Results from all subgroup analyses will be considered supportive and/or hypothesis-generating.

5.6 Multiplicity

The overall study success criterion, agreed upon with FDA, is to simultaneously observe $p \leq 0.01$ for the primary endpoint (NICCE) and $p \leq 0.05$ for the conditional co-primary endpoint (CCPE). Therefore, there is no concern regarding type 1 error inflation due to multiplicity for the overall study success criterion.

To control type 1 error for the key secondary efficacy endpoint, superiority of Reltecimod relative to placebo in terms of freedom from durable loss of renal function among those presenting with Stage 2 or Stage 3 AKI will only be interpreted as a confirmatory hypothesis test if $p \leq 0.01$ for the primary endpoint (NICCE) and $p \leq 0.05$ for the co-primary endpoint (CCPEP). Otherwise, treatment group comparisons in terms of the key secondary efficacy (AKI) endpoint will be interpreted as a descriptive endpoint. An unadjusted chi-square test using a two-sided type 1 error of $\alpha = 0.05$ will be used to test superiority of Reltecimod relative to placebo for the key secondary AKI endpoint.

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[13] Anaya, D. A., E. M. Bulger, et al. Predicting Death in Necrotizing Soft Tissue Infections: A Clinical Score. Surgical Infections 2009: 10(6): 517-522.

[14] Wong, C. H., L. W. Khin, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004: 32(7): 1535-1541.

There will be no attempt to control type 1 error for other secondary NSTI or AKI endpoints.

5.7 Descriptive Analyses of Additional Secondary Endpoints

Additional secondary endpoints have been specified from several domains including individual components of the primary composite endpoint (NICCE), time to resolution of organ dysfunction, critical care and hospital stay parameters (ICU and ICU-free days, ventilator days and –free days, vasopressor days and –free days, hospital LOS), clinical local parameters (debridement history variables), and clinical systemic parameters (mSOFA over time, incidence and recovery from AKI). Analyses for these endpoints will generally be descriptive, with emphasis on characterizing clinical effect sizes[15]. Nominal p-values will be presented in some cases as an aid to interpretation but with no adjustment for multiplicity. 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 compared 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. The c-stat is the probability that a randomly selected patient treated with Reltecimod has a better (e.g., greater number of free-days) than a randomly selection patient treatment with placebo. Methods appropriate for time-to-event endpoints including survival and life-table methods will be used for time-to-organ dysfunction resolution endpoints. Additional analyses of mSOFA over time will employ methods appropriate for longitudinal data. For these analyses, statistical testing and estimation will be based on a Mixed Model Repeated Measures (MMRM)[16].

5.8 Analysis of Longitudinal Outcomes

Supporting analysis will be performed for mSOFA over time using the Mixed Model for Repeated Measures (MMRM) analysis of covariance (ANCOVA) approach[17]. The following baseline covariates will be included in the primary MMRM analysis to mSOFA over time.

- Day 0 mSOFA = 3-4 versus >4
- Presence versus absence of Fournier's gangrene
- APACHE II score
- mSOFA Day 1
- Presence of Stage 2/3 AKI at Screening

mSOFA Day 1 is included because this score reflects patient status post initial surgery. In addition to this variable, the Day 0 stratification factors are included to reflect the experimental design. Screening APACHE II is included to account for variation in medical status at screening. Presence of Stage 2/3 AKI at screening is included given emerging evidence of its impact on clinical outcomes. Inclusion of covariates can increase power by explaining variance and also help with the implicit imputation of missing values that is inherent in the MMRM approach.

MMRM is a direct likelihood approach that requires specialized statistical software for optimizing the likelihood function. For this study, all MMRM parameters will be estimated using SAS PROC MIXED [SAS Institute[18]]. The MMRM model is notable for its ability to include all available data from all eligible subjects and does not require their exclusion as in 'complete case analysis'

[15] Cohen, J. Statistical power analysis for the behavioral sciences (2nd ed.). New York, Academic Press, 1988.
[16] Verbeke G and Molenberghs G. Linear Mixed Models for Longitudinal Data, New York: Springer, 2000.
[17] Verbeke G and Molenberghs G. Linear Mixed Models for Longitudinal Data, New York: Springer, 2000.
[18] SAS Institute, Cary NC.

or arbitrary assignment of values as in 'last-observation-carried-forward' (LOCF). The MMRM model generally includes a factor for treatment group by time interaction in order to allow group differences in mean value to vary over time. Inclusion of outcome data from all time points informs the implicit imputation of values missing at specific time points through the outcome covariance matrix. Inclusion of baseline covariates has potential for further reduction of potential bias due from missing values.

Specifically, MMRM will be used to compare mean values at each time point between the Reltecimod 0.50 mg/kg dose and placebo with a key emphasis on the Day 14 contrast. Model parameters will be estimated using Restricted Maximum Likelihood[19],[20](REML) as implemented Proc Mixed [SAS Institute[21]]. A generalized Satterthwaite approximation will be used to determine accurate estimates of denominator degrees of freedom for statistical tests[22]. Analyses will characterize changes over time as functions of the baseline value, treatment group, time, and treatment by time interaction. Between-group differences at each time point will be evaluated using contrasts derived from mixed model parameter estimates. This approach produces inferences that are valid under the assumption of 'missing at random' (MAR). MAR based inferences are valid under broader assumptions than complete case analysis or analyses utilizing LOCF[23]. The modeling results will be graphically presented by plotting the individual least squares predicted mean values.

5.9 ITT vs mITT

A modified intent-to-treat (mITT) analysis set will be used in the primary and secondary evaluation of efficacy. This is due to the nature of the disease progression and necessity of surgical confirmatory diagnosis. It therefore cannot be avoided that there will be randomized subjects not belonging to the indicated population. These patients are excluded prior to receiving study medication but after randomization. For such patients their randomized allocation is re-used to preserve with strata balance but not their precise randomization ID to avoid confusion (see plan in Randomization section above).

Generally, the purpose of intent-to-treat (ITT) 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[24]. Therefore, mITT comparisons will be according to randomized treatment assignment and we will attempt to include all mITT patients, regardless of intervention or length of follow-up in the primary efficacy comparison.

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[19] Burton P, Gurrin L, Sly P. Extending the simple linear regression model to account for correlated responses: An introduction to generalized estimating equations and multilevel mixed modelling. 2004. http://espace.library.uq.edu.au/view/UQ:259851

[20] Diggle P, Heagerty P, Liang K-Y, Zeger S. Analysis of Longitudinal Data. Oxford University Press; 2002.

[21] SAS Institute, Proc Mixed, SAS/STAT Software.

[22] Hrong-Tai Fai A, Cornelius PL. Approximate F-tests of multiple degree of freedom hypotheses in generalized least squares analyses of unbalanced split-plot experiments. J Stat Comput Simul. 1996;54(4):363-378.

[23] Rubin DB. Inference and missing data. Biometrika. 1976;63(3):581-592.

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

5.10 Handling of Missing Data

5.10.1 mSOFA Scores

mSOFA scores will be assessed as 1) observed cases, 2) last observation carried forward (LOCF), 3) using MMRM, and 4) categorized and combined with mortality and local activity as part of the primary composite clinical success endpoint, NICCE.

The following will be defined as OBSERVED mSOFA.

1. If a single individual organ score is missing but other scores for that day are non-missing, the organ system that were not evaluated are assumed to be free of organ failure are given a value of zero when determining the sum score.
2. If two or more individual organ scores are missing for mSOFA on Day 14 or earlier, but at least one individual organ score is non-missing, the individual organ scores will be imputed using last observation carried forward. In this case, it is possible that different components come from different visits. This will not be done at Day 21 and Day 28.

The following will defined mSOFA LOCF.

3. If all organ scores are missing on Day 14 or earlier, the mSOFA total score from that day will be imputed using last observation carried forward with the following exception..
    c. LOCF will not be performed after patient death.
    d. Note that LOCF will not be performed for unavailable mSOFA total scores at Day 21 and Day 28.
4. When summarizing the individual organ scores apart from the mSOFA total scores, the same rules as above will apply.

Since LOCF will not be applied to missing mSOFA scores after patient death in analyses that employ LOCF to describe mean values of time, there may be some 'diminishing n' and focus is therefore on morbidity rather than mortality.

In contrast, the mixed model repeated measures analyses (MRMM) will utilize implicitly imputed values for all missing values including those subsequent to patient death.

In categorical analyses including formulation of the primary efficacy endpoint, an mSOFA value that is greater than 1 at Day 14 is considered a primary treatment failure in the same fashion as patient death at any time throughout the 28 day follow-up period. LOCF for SOFA is necessary to guarantee that every patient has a value at Day 14 for use in determining NICCE among patients that are alive at the Day 28 and who have not otherwise failed due to other NICCE components including more than 3 debridements, amputation beyond the first debridement.

5.10.2 Handling of Missing Primary Endpoints

As noted above, it is expected to be able to evaluate NICCE in all patients based on the *a priori* specification for this endpoint. If there are any patients with missing primary endpoints, these subjects will be treated as NICCE and CPPE failures in primary analyses and tipping point sensitivity analyses will be conducted. In these analyses, missing values in each group are separately assumed to be either successes or failures. Treatment group differences are computed

based on all possible combinations of assigning success or failure to NICCE to the patients in the two groups. For example, one scenario will be that all missing Reltecimod observations are failures and all missing placebo observations are successes. The next scenario would have one success and the remaining missing values as failure for Reltecimod and all missing placebo outcomes as successes, etc. For each scenario, the hypothetical p-value for testing the primary effectiveness hypothesis will be determined. If there is more than a very few missing values, these results will be plotted using a dot plot with the number of missings assumed as failures for Reltecimod on the x-axis and the number of missing assumed as failures for placebo on the Y-axis. The dots will be color coded to indicate whether or not the primary statistical conclusion changes under each individual scenario. If the fraction of scenarios in which the statistical conclusion changes is small, the primary results will have been shown to be robust against assumptions concerning missingness. If there is more than a small amount of missing data, multiple imputation of missing endpoints may be performed in additional supporting analyses using the SAS procedures, Proc MI and Proc MI Analyze. However, this is not expected to be necessary.

5.10.3 Mixed Model Repeated Measures

The use of MMRM is another method used to address missing data and is considered an optimal approach in many settings. The use of MMRM results in implicit imputations for missing data which are valid under missing at random (MAR), a more general set of assumptions than 'missing completely at random (MCAR)'. For these analyses, there will be implicit imputation of expected mSOFA after patient death. Methods assuming Not Missing at Random (NMAR) require extensive modelling and sensitivity analyses regarding inherently untestable assumptions concerning the missingness mechanism; and will not be used in these analyses.

5.11 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 28 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 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 also 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 (most accurately and specifically) represents 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.

5.12 Deviations from the Original Statistical Plan

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

6 Safety Analysis

The safety measures for this study are AEs, clinical safety laboratory, physical exam, vital signs, ECG (screening day 0 and day 1 post drug) and SAEs including determination of survival through Day 90. The safety profiles will be compared between Reltecimod and placebo groups using descriptive statistics as appropriate for continuous and categorical safety variables.

6.1 Adverse Events

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 for treatment emergent adverse events (TEAEs) defined as those with onset on day 1 or later. TEASs will also be summarized by relationship to study drug, severity, and whether they are serious.

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/vital signs/ECG 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 Electrocardiogram

ECG data will be reviewed by the principal investigator and by an external independent and blinded cardiologist. The blinded core lab evaluation is referred to as "Central Reader". Results will be summarized for the investigator based and central reader based results.

Electrocardiogram results from screening, immediately post drug administration, 4-6 hours post drug administration, and 12-24 hours post drug administration; and changes from screening will be summarized using the As Treated (Safety) Analysis set. Descriptive statistics will include N, mean, median, standard deviation, minimum, and maximum values. Electrocardiogram characteristics to be summarized include heart rate, RR interval, PR interval, QRS complex time, QT interval, and the QTc interval. The results from the central reader will include the QTcB and QTcF intervals.

ECG abnormalities observed during a study will be encompassed under a reported adverse event describing a clinical syndrome. In these cases, the ECG abnormality itself does not need to be recorded as an adverse event.

Similar to that described for laboratory abnormalities, deterioration in baseline ECG parameters as compared to baseline should only be reported as AEs if they fulfil 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 ECG eCRF with the information on the clinically significant test abnormality.

6.4 Physical Exams

Results from physical exams will be tabulated for the Safety Anaysis Set on screening day 0 ('Normal' vs 'Abnormal') as well as for days 3, 7, and 14. The following systems will be assessed: abdomen; cardiovascular; extremities; eyes, ears, nose, and throat; general appearance; head and neck; lymph nodes; neuorlogical; respiratory; and skin. On days 3, 7, and 14, patients will be categorized according to 'Normal', 'Abnormal, improved or same as screening', 'Abnormal, new or aggrevated' and 'Not done'. These data will be summarized as shift tables from the screening visit with results descriptively compared between the Reltecimod and Placebo drug groups.

6.5 Vital Signs

Vital signs include height, weight, BMI, temperature, systolic BP, diastolic BP, MAP, respiration rate, and heart rate. Height and BMI will be summarized at the screening visit by treatment group. The remaining vital sign variables will be summarized as values and as changes from screening across time (day 1, day 2, day 3, day 7, day 10, day 14, day 21, and day 28), separately by treatment group using N, mean, SD, median, minimim, and maximum values. Vital signs will be summarized for the As Treated (Safety) Analysis Set.

7 Presentation of Enrollment and Baseline Characteristics

7.1 Numbers of Patients by Analysis Set

Table 14.1.1.1 summarizes the numbers of patients screened, randomized, and in each analysis set (ITT, As Treated, mITT, and Per Protocol).

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

Table 14.1.1.3 summarizes the numbers of patients by site, treatment group, and randomization stratum in the As Treated (Safety) analysis set. Randomization strata are defined as follows:

(+,+) = (mSOFA>4, Fournier's) (+,-) = (mSOFA>4, No Fournier's)

(-,+) = (mSOFA=3-4, Fournier's) (-,-) = (mSOFA=3-4, No Fournier's)

Tables 14.1.1.4 and 14.1.1.5 provide the same summaries for the mITT and Per Protocol analysis sets, respectively. Totals across all sites will be provided for both of these tables.

7.2 Demographic and Baseline Disease Characteristics of Cohorts

Demographic and baseline characteristics of each analysis set are summarized in Tables 14.1.2.1, 14.1.2.2, and 14.1.2.3, and 14.1.2.4 for the ITT, AT (safety), mITT, and Per Protocol analysis sets, respectively.

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

7.3 Baseline Microbiology

Table 14.1.3.5 summarizes pathogens in tissue samples and blood cultures, overall and by treatment group. The data used are based on verbatim text.

7.4 Prior and Concomitant Medication

Prior and concomitant medication, lifetime and current medications, will be summarized for the All Treated (Safety) analysis set as are all Safety endpoints.

Table 14.1.4.1 will summarize the numbers (%) of patients with prior ancillary (e.g., non-antimicrobial or non-immunosuppressant) medications by category and by specific medication, overall and by treatment group.

Table 14.1.4.2 will present same for antimicrobial and immunosuppressant medications.

Table 14.1.4.3 will summarize the numbers (%) of patients with concomitant ancillary medications by category and by specific medication by treatment group.

Table 14.1.4.4 will present same for antimicrobial and immunosuppressant medications.

7.5 Medical History

Table 14.1.5.1 will summarize the numbers and percentages of patients that experienced prior medical conditions during their lifetime by body system and specific medical condition, overall and by treatment group.

Table 14.1.5.2 will summarize the numbers and percentages of patients with ongoing medical conditions by body system and specific medical condition by treatment group.

7.6 Presentation of NSTI

A summary of factors related to presentation and diagnosis of NSTI will be provided in Table 14.1.6.1. Table 14.1.6.2 will list extensions of NSTI within initial debridement surgery categories.

7.7 Drug Administration and Timing

Day 1 information regarding time from clinical diagnosis 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. Drug exposure will be summarized in Table 14.1.7.2.

7.8 Patient Disposition and End of Study Status

Table 14.1.8.1 summarizes patient disposition and end of study status by treatment group based on the As Treated (Safety) Analysis Set.

8 Presentation of Efficacy Results

8.1 Primary and Conditional Co-Primary Endpoint in mITT Analysis Set

The numbers and percentages of patients in the mITT analysis for each group meeting the primary efficacy endpoint (NICCE) and the conditional co-primary efficacy endpoint (CCPE) are summarized in Tables 14.2.1.1 and 14.2.1.2, respectively. These tables include the statistical significance of the group difference based on unadjusted two-sided chi-square statistics. Study success requires $p \leq 0.01$ for the primary endpoint and $p \leq 0.05$ for the conditional co-primary endpoint. These tables also provide the estimated treatment group differences for both endpoints as well as the 99% confidence interval for the primary endpoint and the 95% confidence interval for the conditional co-primary endpoint. Figures 1 and 2 will be bar charts that illustrate these primary study results. Figures 3 and 4 will be forest plots that summarize the point estimates and confidence intervals of the endpoints and their components.

Tables 14.2.1.1 and 14.2.1.2 also summarize the components of the NICCE and the conditional co-primary endpoint. P-values are provided for descriptive purposes only since there were no *a priori* hypotheses concerning the components, other than they would generally show group differences in the same direction. 95% confidence intervals are provided in order to facilitate an evaluation of the statistical precision in the estimated group differences.

The components of NICCE are:

- Alive at Day 28
- <=3 debridements through Day 14
- No amputation beyond first debridement
- mSOFA score of <=1 at Day 14
- Reduction of >=3 between baseline and Day 14 in mSOFA

The components of the conditional co-primary endpoint (CCPE) are:

- Alive at Day 28
- <=3 debridements through Day 14
- No amputation beyond first debridement

8.2 Primary and Co-Primary Endpoint in Per Protocol Analysis Set

Tables 14.2.1.3 and 14.2.1.4 repeat the analyses above in the Per Protocol analysis set.

8.3 Evaluation of Site Heterogeneity in Primary Endpoint Treatment Effects

Table 14.2.1.5 provides comparisons of the percentages of patients achieving NICCE by site and treatment group. Site-to-site heterogeneity will be evaluated with these data using a random effects 'meta-analysis approach as described in Section 4.3 above. Table 14.2.1.6 provides the same summary for the conditional co-primary endpoint.

8.4 Evaluation of Stratification Factors

Table 14.2.1.7.1 summarizes the numbers and percentages of subjects achieving the NICCE within each level of the randomized stratification. The generalized linear model stratum adjusted risk difference, 99% confidence interval, and the adjusted p-value is presented for comparison to primary unadjusted results. A test for stratum by treatment group interaction will also be presented.

Table 14.2.1.7.2 provides the same analysis but based on the true stratification status. If there are no subjects that were placed in the incorrect stratum, this table will not be produced.

8.5 Sensitivity Analysis Removing the Reduction in mSOFA Component

Table 14.2.1.8 provides a sensitivity analysis for the primary NICCE endpoint. In this analysis, the requirement that there be at least a 3 point reduction in mSOFA from screening to Day 14 is removed. This was the original formulation of the NICCE endpoint before FDA requested that that the reduction component be included for this trial.

8.6 Distribution of mSOFA scores Over Time

Table 14.2.2.1 summarizes mSOFA and its 5 components over time, from screening to Day 28. Since bilirubin is collected only at screening and at Day 7 and 14, observed SOFA total scores will also be summarized at these three timepoints.

Table 14.2.2.2 provides the same summary after application of last-value-carried forward (LOCF) to Day 14. LOCF was not applied after patient death or for missing Day 21 or Day 28 mSOFA.

Table 14.2.2.3 summarizes changes from Day 0 in mSOFA and in each of its components to Days 1, 2, 3, 7, 10, 14, 21, and 28 without applying LOCF.

Table 14.2.2.4 provides the same summary after application of LOCF to Day 14. This table only summarizes mSOFA to Day 14 because there was no LOCF imputation for missing mSOFA after Day 14 and so the results for Days 21 and 28 are identical to the table summarizing mSOFA without LOCF.

Tables 14.2.2.5 and 14.2.2.6 provides the same summaries for observed and LOCF imputed mSOFA and components to Days 28 and 14, respectively, but for changes from Day 1 rather than Day 0.

The data displayed in Tables 14.2.2.1 to 14.2.2.6 will be graphically displayed in line plots comparing between treatment groups using line plot (Figures 5 to 10) and box and whiskers plots (Figures 11 to 14).

Table 14.2.2.7 will summarize mSOFA and organ specific values at screening, 16 - 24 hours post dose, and changes from screening to 16 – 24 hours post dose.

Table 14.2.2.8 will summarize mSOFA without the Glasgow Coma Score and without the Glasgow Coma Score Among Patients on Ventilation and Medications Affecting GCS to Day 28.

8.7 Time to resolution of mSOFA score to ≤ 1

Life tables for time to resolution of mSOFA score ≤ 1 will be provided in Tables 14.2.3.1 and 14.2.3.2 for the 0.50 mg/kg and placebo treated groups, respectively, to Day 14. Comparative Kaplan-Meier survival curves will be provided in Figure 15.

For these analyses, patients who die prior to Day 14 will be considered censored at one day past Day 14 and assumed to have never achieved mSOFA ≤ 1. Log rank statistic will be used to assess if the distributions of times to symptom resolution differ between treatment groups.

These analyses will be repeated using follow-up through Day 28 in Tables 14.2.3.3 and 14.2.3.4 and in Figure 16. For these analyses, patients who die after Day 14 but prior to Day 28 will be evaluated for meeting the mSOFA≤1 and will be considered a success in these analyses if they achieve mSOFA≤1 (prior to their post Day 14 death).

8.8 MMRM Analyses

Figure 17 will be a line graph of least squares predicted mean values over time based on the mixed model for repeated measures (MMRM). This figure will summarize the MMRM results for values over time.

Figure 18 will be a line graph of least squares predicted mean change values over time based on the mixed model for repeated measures (MMRM). This figure will summarize the MMRM results for values over time.

8.9 Critical care and hospital stay parameters, to be measured until Day 28

The following critical care and hospital stay parameters will be assessed in the mITT analysis set.

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

Because of the expected skewness in the distributions of these parameters, non-parametric Wilcoxon rank sum tests will be used assess the statistical significance of treatment group differences in these parameters. Table 14.2.4.1 will provide summary statistics by treatment groups including mean, median, standard deviation, 25th percentile, 75th percentile, minimum, and maximum values. Analyses will focus on clinical effect sizes. The non-parametric clinical effect size to be used is the concordance statistic (c-stat) determined from a logistic regression. The c-stat is the probability that a randomly selected subject treated with Reltecimod has a better outcome (e.g., more free-days) than a randomly selected placebo subject and is related to the area under a receiver operating characteristic (ROC) curve[25]. Graphical comparisons of distributions between treatment groups will be provided using box and whiskers plots (Figures 19 to 25).

Table 14.2.4.2 will summarize hospital discharge status in the mITT analysis set.

Table 14.2.4.3 will summarize hospital readmissions in the mITT analysis set.

Table 14.2.4.4 will summarize critical care and hospital stay parameters over days 1 to 28 comparing NICCE successes to NICCE failures. Figures 26 to 33 will graphically compare these distributions using box and whiskers plots.

[25] Hanley JA and McNeil BJ. The Meaning and Use of the Area under a Receiver Operating Characteristic Curve (ROC), Radiology 1982: 143: 29-36.

Additional graphical analyses will include displaying the percentages of patients staying in the ICU, needing ventilation, and staying in the hospital over time by treatment group (Figures 34, 35, and 36).

Table 14.2.4.5 will summarize critical care and hospital stay parameters over days 1 to 28 comparing subjects with and without freedom from durable loss of renal function status among patients in the mITT analysis presenting with Stage 2 or Stage 3 AKI.

Tables 14.2.4.6, 14.2.4.7, and 14.2.4.8 repeat the treatment group comparisons of critical care and hospital stay parameters, hospital discharge status, and hospital readmissions, but in the Per Protocol analysis set.

8.10 Clinical local parameters (debridements)

The following debridement secondary endpoints were specified:

- Number of debridement to days 7, 10, 14
- Proportion of patients needing (up to Day 14):
  - only one debridement to control the infection
  - 2 debridements to control the infection
  - 3 debridements to control infection
  - ≥3 debridements to control the infection
  - >3 debridements to control infection

Tables 14.2.5.1 will summarize the cumulative numbers of debridements to Days 7, 10, and 14, using means, medians, standard deviations, and ranges. Wilcoxon rank-sum tests will be provided for descriptive pair-wise group comparisons.

Table 14.2.5.2 will summarize the proportions of patients requiring only one debridement, 2 debridements, 3 debridements, ≥ 3 debridements and > 3 debridements up to an including Day 14 for all patients in the mITT Analysis Set and for both treatment groups. Chi-square tests will be used to assess the degree to which observed treatment difference could be attributable to chance variation.

Figure 37 will graphically display the data from Table 14.2.5.1. Figure 38 will graphically display the data from table 14.2.5.2.

8.11 Freedom from Durable Loss of Renal Function

Tables 14.2.6.1.1 to 14.2.6.6 summarize AKI at pre-dose screening and Maximal AKI determined over the first seven days though independent adjudication.

Tables 14.2.6.2.1 to 14.2.6.2.4 summarize treatment group comparisons of the AKI endpoints at Day 28 including the key secondary endpoint, ***Achieving Freedom from Durable Loss of Renal Function at Day 28*** and the exploratory endpoint, ***Improvement in Durable Loss of Renal Function at Day 28***. The summarized analyses differ with regard to whether there was algorithmic determination (primary) or independent adjudication of reference creatinine (sensitivity analysis) and whether the algorithmic determination of Day 28 status was based on LOCF (primary) or using the mean value over days 14 to 28 (sensitivity analysis). The results from Table 14.2.6.2.1 will contain the results from the key secondary endpoint.

Tables 14.2.6.3.1 to 14.2.6.3.3 summarize treatment group comparisons of the AKI endpoints at Day 14 including ***Achieving Freedom from Durable Loss of Renal Function at Day 14*** and ***Improvement in Durable Loss of Renal Function at Day 14***. The summarized analyses differ with regard to whether there was algorithmic determination or independent adjudication of reference creatinine and whether there was algorithmic or independent adjudication of Day 14 status.

Figure 39 will graphically summarize the percentages of subjects in each group achieving ***Freedom from Durable Loss of Renal Function*** at Days 14 and 28. Similarly, Figure 40 will graphically summarize the percentages of subjects in each group achieving ***Improvement in Durable Loss of Renal Function*** at Days 14 and 28.

Tables 14.2.6.4.1 to 14.2.6.4.2 summarize treatment group comparisons of AKD stage at Day 28. The summarized analyses differ with regard to whether there was algorithmic determination or independent adjudication of reference creatinine.

Tables 14.2.6.5.1 to 14.2.6.5.3 summarize treatment group comparisons of AKD stage at Day 14. The summarized analyses differ with regard to whether there was algorithmic determination or independent adjudication of reference creatinine and whether Day 14 status was determined algorithmically or through independent adjudication.

8.12 C - reactive protein (CRP)

Table 14.3.4.1 summarizes CRP at Screening, at Day 14, and changes from Screening to Day 14 for CRP values by treatment group in the mITT 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 treatment emergent adverse event (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 adverse event categories (SOC) are reported in upper case letters and specific adverse events (PT) 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 Comparisons between those with and without a drug-related AE

Table 14.3.1.12 will provide a comparison of demographic and baseline disease characteristics between actively treatment patients experiencing and not experience at least one drug-related adverse event. This table will only be included if there are at least 5 subjects with at least one drug-related adverse event.

9.1.5 Day 0 Adverse Events

Table 14.3.1.13 provides a summary of specific adverse events occurring prior to study drug initiation. This table is not stratified by drug group.

9.1.6 Adverse Events of Special Interest

Infection and infestation adverse events are of special interest. Table 14.3.1.14 summarizes the incidence rates and event counts for infections and infestations TEAEs by preferred term.

9.1.7 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

		AE Listings
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
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.

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 14.3.2.4 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 baseline, Day 1, Day 2, Day 3, Day 7, and Day 14 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 14.3.2.3 provides the same information but for shifts to Day 14.

9.3 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).

9.4 Electrocardiogram

Table 14.3.6.1 summarizes ECG results at screening and immediately, 4-6 hours, and 12-24 hours post study drug, and changes from screening by treatment group based on investigator provided results.

Table 14.3.6.2 provides the same summary but based on the cardiology central reader.

Table 14.3.6.3 summarizes the number and percentages of patients meeting threshold criteria for QTc ECG evaluations by the investigator in the As Treated (Safety) analysis set.

Table 14.3.6.4 provides the same summary for QTcB ECG evaluations determined through cardiology central reader.

Table 14.3.6.5 provides the same summary for QTcF ECG evaluations determined through cardiology central reader.

9.5 Physical Examinations

Physical exam results will be summarized for the screening visit, Day 3, Day 7 and at Day 14. For each test, the number of patients evaluated, and the numbers and percentages of patients with 'Normal', 'Abnormal, improved or same as screening', 'Abnormal, new or aggravated' and 'Not done' will be tabulated, except for screening when results will be categorized as 'Normal', 'Abnormal' or 'Not done'. Results for the following assessments will be summarized for cardiovascular, respiratory, abdomen, extremities, neurological, and other.

Baseline status will be summarized in Table 14.3.7.1. For each of these tests, changes from the screening to Day 3, Day 7, and Day 14 will be summarized in Table 14.3.7.2, 14.3.7.3, and 14.3.7.4, respectively.

9.6 Term Survival

Tables 14.3.8.1 and 14.3.8.2 summarize survival (mortality) to Day 90 for Reltecimod and Placebo, respectively. Figure 41 provides the corresponding Kaplan-Meier survival curve.

Tables 14.3.8.3, 14.3.8.4, and 14.3.8.5 summarize survival (mortality) from Day 14 to Day 90 comparing subjects with Day 14 mSOFA<=1 to Day 14 mSOFA>1 among all mITT subjects, in the Reltecimod subjects alone and among Placebo subject alone, respectively. Figures, 42, 43, and 44 provide the corresponding Kaplan-Meier survival curves.

10 Subgroup Analysis

As noted above, the following tables will be stratified for the pre-specific subgroups noted above.

In addition, results for the primary endpoint NICCE, the conditional co-primary endpoint (CCPE), and the key secondary (AKI) will be summarized across subgroups using forest plots (Figures 47, 49, and 49).

14.2.1.1	Comparisons of the Percentages of Patients Achieving Primary Composite Clinical Success Endpoint (NICCE) and its Components mITT Analysis Set†
14.2.1.2	Comparisons of the Percentages of Patients Achieving Conditional Co-Primary Endpoint (CCPE) and its Components mITT Analysis Set†
14.2.2.2	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 14 Last Observation Carried Forward (LOCF) mITT Analysis Set†
14.2.2.4	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 14 Change from Day 0 (Screening) - Last Observation Carried Forward (LOCF) mITT Analysis Set†
14.2.2.6	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 14 Change from Day 1 - Last Observation Carried Forward (LOCF) mITT Analysis Set†
14.2.4.1	Critical Care and Hospital Stay Parameters Over Days 1 to 28 By Treatment Group mITT Analysis Set†
14.2.5.1	Cumulative Number of Debridements to Days 7, 10, and 14 By Treatment Group mITT Analysis Set†
14.2.5.2	Percentage of Patients Requiring 1, 2, 3, >=3, and >3 Debridements Through Day 14 By Treatment Group mITT Analysis Set†
14.2.6.2.1	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 28 Algorithmic Determination of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 28 Status Using LOCF[&] Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Algorithmic Reference
14.3.1.1	Summary of Treatment-Emergent Adverse Events (TEAEs) Overall and by Treatment Group As Treated (Safety) Analysis Set†

11 Appendix 1: Table TOC

		Enrollment
1	14.1.1.1	Number of Patients Screened, Randomized, and in Each Analysis Set† By Site
2	14.1.1.2	Number of Patients in Each Analysis Set† By Treatment Group and Site
3	14.1.1.3	Number of Patients by Site, Treatment Group, and Randomization Stratum As Treated (Safety) Analysis Set†
4	14.1.1.4	Number of Patients by Site, Treatment Group, and Randomization Stratum mITT Analysis Set†
5	14.1.1.5	Number of Patients by Site, Treatment Group, and Randomization Stratum Per Protocol Analysis Set†
		Demographic and Baseline Characteristics
6	14.1.2.1	Demographics and Baseline Disease Characteristics Overall and By Treatment Group ITT (Randomized) Set†
7	14.1.2.2	Demographics and Baseline Disease Characteristics Overall and By Treatment Group As Treated (Safety) Analysis Set†
8	14.1.2.3	Demographics and Baseline Disease Characteristics Overall and By Treatment Group mITT Analysis Set†
9	14.1.2.4	Demographics and Baseline Disease Characteristics Overall and By Treatment Group Per Protocol Analysis Set†
10	14.1.3.1	Patients by Gender and Age Category Overall and by Treatment Group ITT (Randomized) Set†
11	14.1.3.2	Patients by Gender and Age Category Overall and by Treatment Group As Treated (Safety) Analysis Set†
12	14.1.3.3	Patients by Gender and Age Category Overall and by Treatment Group mITT Analysis Set†
13	14.1.3.4	Patients by Gender and Age Category Overall and by Treatment Group Per Protocol Analysis Set†
		Summary of Baseline Microbiology
14	14.1.3.5	Pathogen in Tissue Samples & Blood Culture As Treated (Safety) Analysis Set†

		Prior and Concomitant Medications
15	14.1.4.1	Number (%) of Patients with Prior Ancillary Medications by Category and Specific Medication Overall and By Treatment Group As Treated (Safety) Analysis Set†
16	14.1.4.2	Number (%) of Patients with Prior Antimicrobial or Immunosuppressant Medications by Category and Specific Medication Overall and By Treatment Group As Treated (Safety) Analysis Set†
17	14.1.4.3	Number (%) of Patients with Concomitant Ancillary Medications by Category and Specific Medication By Treatment Group As Treated (Safety) Analysis Set†
18	14.1.4.4	Number (%) of Patients with Concomitant Antimicrobial or Immunosuppressant Medications by Category and Specific Medication By Treatment Group As Treated (Safety) Analysis Set†
		Medical
19	14.1.5.1	Number (%) of Patients Experiencing Prior Medical Conditions During Lifetime by Body System and Specific Medical Condition As Treated (Safety) Analysis Set†
20	14.1.5.2	Number (%) of Patients with Ongoing Medical Conditions by Body System and Specific Medical Condition As Treated (Safety) Analysis Set†

		NSTI Presentation
21	14.1.6.1	NSTI Presentation and Initial Debridement Surgery Overall and By Treatment Group mITT Analysis Set†
22	14.1.6.2	NSTI Primary Infection Location and Extension of Infection Overall and By Treatment Group mITT Analysis Set†
		Drug Timing and Administration
23	14.1.7.1	Drug Administration and Timing Overall and by Treatment Group As Treated (Safety) Analysis Set†
24	14.1.7.2	Extent of Drug Exposure Reltecimod 0.5 mg/kg As Treated (Safety) Analysis Set†
		Patient Disposition and End of Study
25	14.1.8.1	Patient Disposition and End of Study Status By Treatment Group As Treated (Safety) Analysis Set†

		Efficacy Analyses
		Primary and Conditional Co-Primary Endpoints
26	14.2.1.1	Comparisons of the Percentages of Patients Achieving Primary Composite Clinical Success Endpoint (NICCE) and its Components By Treatment Group mITT Analysis Set†
27	14.2.1.2	Comparisons of the Percentages of Patients Achieving Conditional Co-Primary Endpoint (CCPE) and its Components By Treatment Group mITT Analysis Set†
28	14.2.1.3	Comparisons of the Percentages of Patients Achieving Primary Composite Clinical Success Endpoint (NICCE) and its Components By Treatment Group Per Protocol Analysis Set†
29	14.2.1.4	Comparisons of the Percentages of Patients Achieving Conditional Co-Primary Endpoint (CCPE) and Its Components By Treatment Group Per Protocol Analysis Set†
30	14.2.1.5	Comparisons of the Percentages of Patients Achieving the Primary Composite Clinical Success Endpoint (NICCE) By Treatment Group and Site mITT Analysis Set†
31	14.2.1.6	Comparisons of the Percentages of Patients Achieving the Conditional Co-Primary Endpoint (CCPE) By Treatment Group and Site mITT Analysis Set
32	14.2.1.7.1	Comparisons of the Percentages of Patients Achieving Primary Composite Clinical Success Endpoint (NICCE*) by Randomization Stratification By Treatment Group mITT Analysis Set†
33	14.2.1.7.2	Comparisons of the Percentages of Patients Achieving Primary Composite Clinical Success Endpoint (NICCE*) by True Baseline mSOFA and Fournier's Status By Treatment Group mITT Analysis Set†
34	14.2.1.8	Comparisons of the Percentages of Patients Achieving Modified NICCE Endpoint with the Reduction in mSOFA Component Removed By Treatment Group mITT Analysis Set†
		SOFA
35	14.2.2.1	Modified SOFA Total Score, Organ Specific Scores, and SOFA Total Score Over Time to Day 28 Observed Cases By Treatment Group mITT Analysis Set†
36	14.2.2.2	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 14 By Treatment Group

		Last Observation Carried Forward (LOCF) By Treatment Group mITT Analysis Set†
37	14.2.2.3	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 28 Change from Day 0 (Screening) - Observed Cases By Treatment Group mITT Analysis Set†
38	14.2.2.4	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 14 Change from Day 0 (Screening) - Last Observation Carried Forward (LOCF) By Treatment Group mITT Analysis Set†
38	14.2.2.5	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 28 Change from Day 1 - Observed Cases By Treatment Group mITT Analysis Set†
40	14.2.2.6	Modified SOFA Total Score and Organ Specific Scores Over Time to Day 14 Change from Day 1 - Last Observation Carried Forward (LOCF) By Treatment Group mITT Analysis Set†
41	14.2.2.7	Modified SOFA Total Score and Organ Specific Screening, 16 to 24 Hours Post Dose, and Changes from Screening to 16-24 Hours Post Dose Observed cases By Treatment Group mITT Analysis Set
42	14.2.2.8	Modified SOFA Total Score without Glasgow Coma Score and without Glasgow Coma Score Among Patients on Ventilation and Medications Affecting GCS to Day 28 Observed cases By Treatment Group mITT Analysis Set
43	14.2.3.1	Life Table Analysis to Day 14 Time to Resolution of Organ Dysfunction (mSOFA<=1) Reltecimod 0.5 mg/kg mITT Analysis Set†
44	14.2.3.2	Table 14.2.3.2 Life Table Analysis to Day 14 Time to Resolution of Organ Dysfunction (mSOFA<=1) Placebo mITT Analysis Set†
45	14.2.3.3	Life Table Analysis to Day 28 Time to Resolution of Organ Dysfunction (mSOFA<=1) Reltecimod 0.5 mg/kg mITT Analysis Set†
46	14.2.3.4	Life Table Analysis to Day 28 Time to Resolution of Organ Dysfunction (mSOFA<=1) Placebo mITT Analysis Set†

		Critical Care and Hospital Stay
47	14.2.4.1	Critical Care and Hospital Stay Parameters Over Days 1 to 28 By Treatment Group mITT Analysis Set†
48	14.2.4.2	Hospital Discharge Status By Treatment Group mITT Analysis Set†
49	14.2.4.3	Hospital Readmissions By Treatment Group, Safety Analysis Set mITT Analysis Set
50	14.2.4.4	Critical Care and Hospital Stay Parameters Over Days 1 to 28 By NICCE* Success vs. Failure mITT Analysis Set†
51	14.2.4.5	Critical Care and Hospital Stay Parameters Over Days 1 to 28 By Freedom from Durable Loss of Renal Function Status Among Subjects Presenting with AKI Stage 2 or 3 mITT Analysis Set†
52	14.2.4.6	Critical Care and Hospital Stay Parameters Over Days 1 to 28 By Treatment Group Per Protocol Analysis Set†
53	14.2.4.7	Hospital Discharge Status By Treatment Group Per Protocol Analysis Set†
54	14.2.4.8	Hospital Readmissions By Treatment Group, Safety Analysis Set Per Protocol Analysis Set
		Debridement Outcomes
55	14.2.5.1	Cumulative Number of Debridements to Days 7, 10, and 14 By Treatment Group mITT Analysis Set†
56	14.2.5.2	Percentage of Patients Requiring 1, 2, 3, >=3, and >3 Debridements Through Day 14 By Treatment Group mITT Analysis Set†

		Analyses of AKI
		Screening AKI and Maximal AKI
57	14.2.6.1.1	Comparisons of Percentages of Subjects With Each AKI Stage at Pre-Dose Screening by Algorithmic Determination By Treatment Group mITT Analysis Set†
58	14.2.6.1.2	Numbers and Percentages of Subjects With Any AKI and with AKI Stage 2 or 3 Based on Screening AKI by Algorithmic Determination By Treatment Group mITT Analysis Set†
59	14.2.6.1.3	Comparisons of Percentages of Subjects With Each Maximal AKI Stage by Independent Adjudication By Treatment Group mITT Analysis Set†
60	14.2.6.1.4	Numbers and Percentages of Subjects With Any AKI and with AKI Stage 2 or 3 Based on Maximal AKI by Independent Adjudication By Treatment Group mITT Analysis Set†
61	14.2.6.1.5	Comparisons between AKI Stage at Screening and Maximal AKI Using Algorithmic Reference for AKI Stage at Screening By Treatment Group mITT Analysis Set†
62	14.2.6.1.6	Comparisons between AKI Stage at Screening and Maximal AKI Using Independent Adjudicated Reference for AKI Stage at Screening By Treatment Group mITT Analysis Set†
		Day 28 Endpoints
63	14.2.6.2.1	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 28 Algorithmic Determination of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 28 Status Using LOCF Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Algorithmic Reference
64	14.2.6.2.2	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 28 Independent Adjudication of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 28 Status Using LOCF Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Adjudicated Reference
65	14.2.6.2.3	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 28 Algorithmic Determination of Reference Creatinine Algorithmic Determination of AKI at Screening

		Algorithmic Determination of Day 28 Status Using Mean of Day 14 to Day 28 Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Algorithmic Reference
66	14.2.6.2.4	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 28 Independent Adjudication of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 28 Status Using Mean of Day 14 to Day 28 Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Adjudicated Reference
		Day 14 Endpoints
67	14.2.6.3.1	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 14 Algorithmic Determination of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 14 Status Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Algorithmic Reference
68	14.2.6.3.2	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 14 Independent Adjudication of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 14 Status Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Adjudicated Reference
69	14.2.6.3.3	Numbers and Percentages of Subjects Achieving Freedom from Durable Loss of Renal Function and Improvement in Durable Loss of Renal Function at Day 14 Independent Adjudication of Reference Creatinine Algorithmic Determination of AKI at Screening Independent Adjudication of Day 14 Status[&] Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Adjudicated Reference
		AKD Stages at Day 28
70	14.2.6.4.1	Numbers and Percentages of Subjects with Specific AKD Stages at Day 28 Algorithmic Determination of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 28 Status Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Algorithmic Reference
71	14.2.6.4.2	Numbers and Percentages of Subjects with Specific AKD Stages at Day 28 Independent Adjudication of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 28 Status Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Adjudicated Reference
		AKD Stages at Day 14
72	14.2.6.5.1	Numbers and Percentages of Subjects with Specific AKD Stages at Day 14 Algorithmic Determination of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 14 Status

		Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Algorithmic Reference
73	14.2.6.5.2	Numbers and Percentages of Subjects with Specific AKD Stages at Day 14 Independent Adjudication of Reference Creatinine Algorithmic Determination of AKI at Screening Algorithmic Determination of Day 14 Status[&] Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Adjudicated Reference
74	14.2.6.5.3	Numbers and Percentages of Subjects with Specific AKD Stages at Day 14 Independent Adjudication of Reference Creatinine Algorithmic Determination of AKI at Screening Independent Adjudication of Day 14 Status[&] Among mITT Subjects with Stage 2 or Stage 3 Screening AKI Using Adjudicated Reference

		Adverse Events
75	14.3.1.1	Summary of Treatment-Emergent Adverse Events (TEAEs) By Treatment Group As Treated (Safety) Analysis Set†
76	14.3.1.2	Incidence Rates (%) and Event Counts of TEAEs by System Organ Class and Preferred Term By Treatment Group As Treated (Safety) Analysis Set†
77	14.3.1.3	Incidence Rates (%) and Event Counts of TEAEs Sorted by Descending Incidence of Preferred Term As Treated (Safety) Analysis Set†
78	14.3.1.4	Incidence Rates (%) and Event Counts of Drug-Related* TEAEs by System Organ Class and Preferred Term As Treated (Safety) Analysis Set†
79	14.3.1.5	Incidence Rates (%) and Event Counts of Serious TEAEs by System Organ Class and Preferred Term As Treated (Safety) Analysis Set†
80	14.3.1.6	Incidence Rates (%) and Events Counts of Serious TEAEs Sorted by Descending Incidence of Preferred Term in Subjects Receiving Reltecimod As Treated (Safety) Analysis Set†
81	14.3.1.7	Incidence Rates (%) and Events Counts of Serious Drug-Related* TEAEs by System Organ Class and Preferred Term As Treated (Safety) Analysis Set†
82	14.3.1.8	Incidence Rates (%) and Events Counts of Severe TEAEs by System Organ Class and Preferred Term As Treated (Safety) Analysis Set†
83	14.3.1.9	Incidence Rates (%) and Events Counts of Severe TEAEs Sorted by Descending Incidence of Preferred Term in Subjects Receiving Reltecimod As Treated (Safety) Analysis Set†
84	14.3.1.10	Counts of Drug-Related* TEAEs by Severity, System Organ Class, and Preferred Term Reltecimod 0.5 mg/kg As Treated (Safety) Analysis Set†
85	14.3.1.11	Counts of Drug-Related* TEAEs by Severity, System Organ Class, and Preferred Term Placebo As Treated (Safety) Analysis Set†
86	14.3.1.12	Demographic and Baseline Disease Characteristics of Patients With and Without a Drug-Related TEAE in As Treated (Safety) Analysis Set Receiving Reltecimod 0.5 mg/kg
87	14.3.1.13	Incidence Rates (%) and Event Counts of AEs by System Organ Class and Preferred Term on Day 0 Prior to Drug Administration As Treated (Safety) Analysis Set†
88	14.3.1.14	Incidence Rates (%) and Events Counts of Infections and Infestations TEAEs by Preferred Term As Treated (Safety) Analysis Set†

		Laboratory Data
89	14.3.2.1	Screening, Day 7, Day 14, and Changes from Screening Blood Chemistry by Treatment Group As Treated (Safety) Analysis Set†
90	14.3.2.2	Blood Chemistry Panel Shift Tables Summarizing Changes in Test Status from Screening (Baseline) to Day 7 or Early Discontinuation As Treated (Safety) Analysis Set†
91	14.3.2.3	Blood Chemistry Panel Shift Tables Summarizing Changes in Test Status from Screening (Baseline) to Day 14 or Early Discontinuation As Treated (Safety) Analysis Set†
92	14.3.2.4	Summary of Potential Drug Induced Liver Injury (DILI) By Treatment Group As Treated (Safety) Analysis Set†
93	14.3.2.5	Blood Chemistry Frequencies By Visit With Respect To Normal Ranges and Critical Values by Treatment Group As Treated (Safety) Analysis Set†
94	14.3.3.1	Screening, Days 1, 2, 3, 7 and 14, and Changes from Screening Blood Hematology by Treatment Group As Treated (Safety) Analysis Set†
95	14.3.3.2	Blood Hematology Panel Shift Tables Summarizing Changes in Test Status from Screening (Baseline) to Day 7 Early Discontinuation
96	14.3.3.3	Blood Hematology Panel Shift Tables Summarizing Changes in Test Status from Screening (Baseline) to Day 14 Early Discontinuation
97	14.3.3.4	Blood Hematology Frequencies by Visit with Respect to Normal Ranges and Critical Values by Treatment Group As Treated (Safety) Analysis Set
		C-Reactive Protein
98	13.3.4.1	C-Reactive Protein at Screening and Day 14, and Changes from Screening by Treatment Group mITT Analysis Set†
		Vital Signs
99	14.3.5.1	Vital Signs at Screening, Day 1, Day 2, Day 3, Day 7, Day 14, Day 21, Day 28 and Changes from Screening By Treatment Group As Treated (Safety) Analysis Set†

		ECG
100	14.3.6.1	Screening, Immediately Post Dose, 4-6 Hours, and 12-24 Hours Post Study Drug Electrocardiogram Results Evaluated by Investigator by Treatment Group As Treated (Safety) Analysis Set†
101	14.3.6.2	Screening, Immediately Post Dose, 4-6 Hours, and 12-24 Hours Post Study Drug Electrocardiogram Results Evaluated by Central Reader by Treatment Group As Treated (Safety) Analysis Set†
102	14.3.6.3	Number (%) of Patients Meeting Threshold Criteria for QTc ECG Results Evaluated by Investigator As Treated (Safety) Analysis Set†
103	14.3.6.4	Number (%) of Patients Meeting Threshold Criteria for QTcB ECG Results Evaluated by Central Reader As Treated (Safety) Analysis Set†
104	14.3.6.5	Number (%) of Patients Meeting Threshold Criteria for QTcF ECG Results Evaluated by Central Reader As Treated (Safety) Analysis Set†
		Physical Exam
105	14.3.7.1	Physical Exam Assessments at Screening Overall and By Treatment Group As Treated (Safety) Analysis Set†
106	14.3.7.2	Summary of Physical Exam Assessments at Screening and at Day 3 Overall and By Treatment Group As Treated (Safety) Analysis Set†
107	14.3.7.3	Summary of Physical Exam Assessments at Screening and at Day 7 Overall and By Treatment Group As Treated (Safety) Analysis Set†
108	14.3.7.4	Summary of Physical Exam Assessments at Screening and at Day 14 Overall and By Treatment Group As Treated (Safety) Analysis Set†
		Survival
109	14.3.8.1	Life Table Analysis to Day 90, Mortality - Reltecimod 0.50 mg/kg, mITT Analysis Set
110	14.3.8.2	Life Table Analysis to Day 90, Mortality - Placebo, mITT Analysis Set
111	14.3.8.3	Life Table Analysis from Day 14 to Day 90 Comparing Subjects with Day 14 mSOFA<=1 to Day 14 mSOFA>1 mITT analysis Set - Pooled
112	14.3.8.4	Life Table Analysis from Day 14 to Day 90 Comparing Subjects with Day 14 mSOFA<=1 to Day 14 mSOFA>1 mITT analysis Set - Reltecimod
113	14.3.8.5	Life Table Analysis from Day 14 to Day 90 Comparing Subjects with Day 14 mSOFA<=1 to Day 14 mSOFA>1 mITT analysis Set - Placebo

12 Appendix 2: AE Listings TOC

		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
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

13 Appendix 3: Patient Listings TOC

		Patient Listings
1	16.2.8.1	Form: Demographics
2	16.2.8.2	Form: Medical History
3	16.2.8.3	Form: Vital Signs
4	16.2.8.4	Form: Physical Exam
5	16.2.8.5	Form: Necrotizing Soft Tissue Infection Information
6	16.2.8.6	Form: Primary Infection Site Assessment
7	16.2.8.7	Form: Initial Debridement
8	16.2.8.8	Form: Modified SOFA (mSOFA)
9	16.2.8.9	Form: Glasgow Coma Score
10	16.2.8.10	Form: Drug Randomization and Administration
11	16.2.8.11	Form: Blood Culture
12.1	16.2.8.12.1	Form: Tissue Microbiology
12.2	16.2.8.12.2	Pathogen Assignment (Tissue and Blood Culture)
13	16.2.8.13	Form: 12-Lead ECG (Screening)
14	16.2.8.14	Form: 12-Lead Electrocardiogram (Post Drug)
14.1	16.2.8.14.1	Post drug ECG Among Subjects with >500 msec and/or >60 msec from baseline Cardiology Overread QTcB
14.2	16.2.8.14.2	Post drug ECG Among Subjects with >500 msec and/or >60 msec from baseline Cardiology Overread QTcF
15	16.2.8.15	Form: Month 3 Visit Status
16	16.2.8.16	Form: Chemistry1
17	16.2.8.17	Form: Hematology
18	16.2.8.18	Form: C-Reactive Protein
19	16.2.8.19	Form: Chemistry 2
20	16.2.8.20	Form: Apache
21	16.2.8.21	Form: LRINEC and Anaya Score Parameters
22	16.2.8.22	Form: Follow-up Lesion Assessment
23	16.2.8.23	Form: ICU Admission/Discharge
24	16.2.8.24	Form: Adequacy of Microbial Treatment
25	16.2.8.25	Form: Follow-Up Debridement
26	16.2.8.26	Form: Amputation

27	16.2.8.27	Form: Urine Output
28	16.2.8.28	Form: Renal Replacement Therapy
29	16.2.8.29	Form: Transfusion History
30	16.2.8.30	Form: Ventilator Assistance - Log
31	16.2.8.31	Form: Hyperbaric Oxygen
32	16.2.8.32	Form: Plasmapheresis
33	16.2.8.33	Form: ICU Admittance
34	16.2.8.34	Form: Hospital Length of Stay
35	16.2.8.35	Form: Hospital Readmission
36	16.2.8.36	Form: Prior and Concomitant Ancillary Medications
37	16.2.8.37	Form: Prior and Concomitant Antimicrobial and Immunosuppressant Medications
38	16.2.8.38	Form: Death Form
39	16.2.8.39	Form: End of Study/Early Discontinuation
40	16.2.8.40	Form: Pregnancy

14 Appendix 4: Figures TOC

Figure	*Topic*	*Type of Graph*	*Showing*	*Data Source*
1	NICCE	Bar graph	Percent of Patients Achieving Primary Efficacy Endpoint in (NICCE) in mITT Analysis Set	Table 14.2.1.1
2	CCPE	Bar graph	Percent of Patients Achieving Conditional Co-Primary Endpoint (CCPE) in mITT Analysis Set	Table 14.2.1.2
3	NICCE and Components	Forrest Plot	99% CI for NICCE and 95% CI's for Components of NICCE	Table 14.2.1.1
4	Conditional Co-Primary and Components	Forrest Plot	95% CI for conditional co-primary and components	Table 14.2.1.2
5	mSOFA	Line plot	mSOFA Over Time to Day 28 - Observed cases	Table 14.2.2.1
6	mSOFA	Line plot	mSOFA Over Time to Day 14 - LOCF	Table 14.2.2.2
7	mSOFA	Line plot	mSOFA Over Time to Day 28 Change From Day 0 (Screening) - Observed Cases	Table 14.2.2.3
8	mSOFA	Line plot	mSOFA Over Time to Day 14 Change From Day 0 (Screening) - LOCF	Table 14.2.2.4
9	mSOFA	Line plot	mSOFA Over Time to Day 28 Change From Day 1 - Observed cases	Table 14.2.2.5
10	mSOFA	Line plot	mSOFA Over Time to Day 14 Change From Day 1 - LOCF	Table 14.2.2.6
11	mSOFA	Box and Whiskers	Reltecimod vs Placebo mSOFA at Day 14 – Observed cases	Table 14.2.2.1
12	mSOFA	Box and Whiskers	Reltecimod vs Placebo mSOFA at Day 14 – LOCF	Table 14.2.2.2
13	mSOFA	Box and Whiskers	Reltecimod vs Placebo mSOFA at Day 21 – Observed cases	Table 14.2.2.3
14	mSOFA	Box and Whiskers	Reltecimod vs Placebo mSOFA at Day 28 – Observed cases	Table 14.2.2.5
14	mSOFA	Kaplan-Meier survival curves	Comparing Time to mSOFA <=1 censored at Day 14	Table 14.2.3.1 Table 14.2.3.2
16	mSOFA	Kaplan-Meier survival curves	Comparing Time to mSOFA <=1 to Day 28	Table 14.2.3.3 Table 14.2.3.4
17	mSOFA	Line graph	Least squares predicted mean mSOFA over time based on the mixed model for repeated measures (MMRM).	Table 14.2.2.1
18	mSOFA	Line graph	Least squares predicted mean change in mSOFA over time based on the mixed model for repeated measures (MMRM).	Table 14.2.2.3
19	Critical care and hospital stay	Box and Whiskers	ICU free days By Treatment Group	Table 14.2.4.1
20	Critical care and hospital stay	Box and Whiskers	Days in ICU By Treatment Group	Table 14.2.4.1
21	Critical care and hospital stay	Box and Whiskers	Days on ventilator By Treatment Group	Table 14.2.4.1
22	Critical care and hospital stay	Box and Whiskers	Ventilator free days By Treatment Group	Table 14.2.4.1
23	Critical care and hospital stay	Box and Whiskers	Vasopressors days By Treatment Group	Table 14.2.4.1
24	Critical care and hospital stay	Box and Whiskers	Vasopressors free days By Treatment Group	Table 14.2.4.1
25	Critical care and hospital stay	Box and Whiskers	Hospital Length of Stays By Treatment Group	Table 14.2.4.1
26	Critical care and hospital stay	Box and Whiskers	ICU free days By NICCE Success versus Failure	Table 14.2.4.3
27	Critical care and hospital stay	Box and Whiskers	Days in ICU By NICCE Success versus Failure	Table 14.2.4.3
28	Critical care and hospital stay	Box and Whiskers	Days on ventilator By NICCE Success versus Failure	Table 14.2.4.3
29	Critical care and hospital stay	Box and Whiskers	Ventilator free days By NICCE Success versus Failure	Table 14.2.4.3
30	Critical care and hospital stay	Box and Whiskers	Vasopressors days By NICCE Success versus Failure	Table 14.2.4.3
31	Critical care and hospital stay	Box and Whiskers	Vasopressors free days By NICCE Success versus Failure	Table 14.2.4.3
32	Critical care and hospital stay	Box and Whiskers	Hospital Length of Stay By NICCE Success versus Failure	Table 14.2.4.3
33	Critical care and hospital stay	Box and Whiskers	Hospital Length of Stay By NICCE Success versus Failure	Table 14.2.4.4

Figure	*Topic*	*Type of Graph*	*Showing*	*Data Source*
34	Critical care and hospital stay	Line graph	% of patients staying in ICU over time by treatment group	Figure34.sas
35	Critical care and hospital stay	Line graph	% of patients needing ventilation over time by treatment group	Figure35.sas
36	Critical care and hospital stay	Line graph	% of patients staying at Hospital over time	Figure36.sas
37	Debridement	Bar chart with mean (SD)	Cumulative Numbers of Debridements to Days 7, 10, 14, and 28 Overall and by Treatment Group By Treatment Group	Table 14.2.5.1
38	Debridement	Bar graphs with %'s and Fisher's p-values.	Percentages of Patients Requiring 1, 2, ≥ 2, and ≥ 3 Debridements Though Day 14, By Treatment Group	Table 14.2.5.2
39	AKI	Bar graph	Percent of patients Achieving Freedom from Durable Loss of Renal Function	Table 14.2.6.2.1 Table 14.2.6.3.1
40	AKI	Bar graph	Percent of patients Achieving Improvement in Durable Loss of Renal Function at Day 14 and at Day 28	Table 14.2.6.2.1 Table 14.2.6.3.1
41	Mortality	Kaplan-Meier	Mortality to Day 90	Table 14.3.8.1 Table 14.3.8.2
42	Mortality	Kaplan-Meier	Mortality from Day 14 to Day 90 Comparing mSOFA<=1 at Day 14 to mSOFA>1 at Day 14 - Pooled	Table 14.3.8.3
43	Mortality	Kaplan-Meier	Mortality from Day 14 to Day 90 Comparing mSOFA<=1 at Day 14 to mSOFA>1 at Day 14 - Reltecimod	Table 14.3.8.4
44	Mortality	Kaplan-Meier	Mortality from Day 14 to Day 90 Comparing mSOFA<=1 at Day 14 to mSOFA>1 at Day 14 - Placebo	Table 14.3.8.5
45	NICCE and Components	Forrest Plot	99% CI for NICCE and 95% CI's for Components of NICCE	Table 14.2.1.1
46	Conditional Co-Primary and Components	Forrest Plot	95% CI for conditional co-primary and components	Table 14.2.1.2
47	NICCE	Forrest Plot	Point estimates and 95% CI for NICCE in subgroups	Stratified versions of Table 14.2.1.1
48	CCPE	Forrest Plot	Point estimates and 95% CI for CCPE in subgroups	Stratified versions of Table 14.2.1.2
49	AKI endpoint	Forrest Plot	Point estimates and 95% CI for AKI endpoint in subgroups	Stratified versions of Table 14.2.6.3

15 Appendix 5: Clinical Score Calculations

Clinical Scores Parameters			
Parameter	LRINEC	Anaya	SOFA
Clinical			
Cardiovascular system (Mean Arterial Pressure calculation)			+
Heart Rate		+	
Nervous system (Glasgow Coma Score)			+
Oxygenation *(Calculation)*			+ (PaO_2/FiO_2)
Temperature		+	
Demographics			
Age		+	
Laboratory			
Coagulation Function (Platelets)			+
C-Reactive Protein	+		
Renal system / Creatinine	+	+	+
Glucose	+		
Hemoglobin/Hematocrit	+	+	
Liver Function Test / Bilirubin			+
Sodium	+		
Total white cell count	+	+	

SOFA – Sequential Organ Failure Assessment score

Can range from 0 -24

Respiratory system:

PaO_2 / FiO_2 (mmHg)	**SOFA score**
=>400	0
< 400	1
< 300	2
< 200 and mechanically ventilated	3
< 100 and mechanically ventilated	4

Nervous System:

Glasgow Coma Scale	**SOFA score**
15	0
13-14	1
10-12	2
6-9	3
< 6	4

Cardiovascular System

Mean Arterial Pressure (MAP) OR administration of vasopressors (mcg/Kg/minute)	**SOFA score**
MAP => 70 mmHg	0
MAP < 70 mmHg	1
Dopamine <= 5 OR Dobutamine any dose	2
Dopamine > 5 <=15 OR epinephrine <=0.1 OR norepinephrine <= 0.1	3
Dopamine > 15 OR epinephrine > 0.1 OR norepinephrine > 0.1	4

MAP= (Systolic pressure + (2*Diastolic pressure))/3

Liver:

Bilirubin (mg/dl)	**SOFA score**
<1.2	0
1.2-1.9	1
2.0-5.9	2
6.0-11.9	3
>= 12.0	4

Coagulation:

Platelets x 10^3/mcl	**SOFA score**
=>150	0
< 150	1
< 100	2
< 50	3
< 20	4

Renal System:

Creatinine (mg/dl) (or urine output)	**SOFA score**
<1.2	0
1.2 – 1.9	1
2.0 – 3.4	2
3.5 – 4.9 (or < 500 ml/day)	3
>=5.0 (or < 200 ml/day)	4

Anaya score

Can range from 0 - 12

Variable on admission	**Points**
Heart Rate > 110 beats per minute	1
Temperature < 36.0 ^{0}C	1
Serum Creatinine > 1.5 mg/dl	1
Age > 50	3
White blood cells count > 40,000/mcl	3
Hematocrit > 50%	3

LRINEC – Laboratory Risk Indicator for Necrotizing Fasciitis

Can range from 0 – 13

Variable, Units	Score
C-Reactive Protein mg/L	
< 150	0
>= 150	4
Total White Blood cells count per mm^3	
< 15	0
15 - 25	1
>25	2
Hemoglobin g/dL	
>13.5	0
11.0 – 13.5	1
< 11	2
Sodium mmol/L or meq/L	
>= 135	0
< 135	2
Creatinine µmol/L (mg/dL)	
<= 141 (1.595)	0
>141 (1.595)	2
Glucose mmol/L (mg/dL)	
<=10 (180.18)	0
>10 (180.18)	1

16 Appendix 6: Randomization Program: SAS call to R program

```
proc format;
 value treatment_fmt
   1 = 'Placebo'
   2 = 'Active'
 ;
run;

proc iml;
submit / R;

library(doParallel)
site_hold <- seq(10,49, by = 1)
strata_hold <- c(1,2,3,4)
block_4 <- c(1,1,2,2)
block_6 <- c(1,1,1,2,2,2)

theseed = 42
set.seed(theseed)
site_loop <- foreach (si = site_hold, .combine=rbind) %do% {
  site_num <- si

  strata_loop <- foreach (s = strata_hold, .combine=rbind) %do% {
    strata_num <- s

    full_block <- foreach (i =1:5, .combine=rbind) %do% {
      get_random_block <- rbinom(1, 1, 0.5)

      if (get_random_block == 1) {
        block <- sample(block_6, 6, replace = FALSE)
      }

      if (get_random_block == 0) {
        block <- sample(block_4, 4, replace = FALSE)
      }

      full_block <- as.matrix(block)
    }
    strata <- rep(s, length(full_block))
    seqnum <- seq(1,(length(full_block)), by = 1)

    strata_seq_treat <- cbind(strata,seqnum, full_block)

  }
  site <- rep(site_num, nrow(strata_loop))
  with_site <-cbind(strata_loop, site)

}

site_loop_df <- as.data.frame(site_loop)
seq_num      <- sprintf("%02d", as.numeric(site_loop_df$seqnum))

seed <- rep(theseed, nrow(site_loop_df))
```

```
random_id   <- cbind(paste(site_loop_df$site, site_loop_df$strata, seq_num,
 sep=''))
full_random <- cbind(site_loop_df$site, site_loop_df$strata, seq_num,
 site_loop_df$V3, seed)


endsubmit;

run importdatasetfromr ("random_id", "random_id");
run importdatasetfromr ("full_random", "full_random");
quit;

data full_random;
 formerge + 1;
 set full_random;
 rename v1 = site;
 rename v2 = strata;
 rename v4 = treatment;
run;

data random_id;
 set random_id;
 formerge + 1;
run;

data randomid;
 merge random_id full_random;
 by formerge;
 rename v1 = randomid;

 label
   v1 = 'RandomID'
   site = 'Site Number (10-49)'
   strata = 'Strata Number (1-4)'
   seq_num = 'Number of patient (1- ~26)'
   /*v3 = 'Treatment (1/2)'*/
   treatment = 'Treatment (Placebo/Active)'
   seed = 'Seed'
 ;

 drop formerge;
 format treatment treatment_fmt.;
run;


title1 'ATXBIO';
title2 'Randomization';

%macro to_excel(site);
%do i = 10 %to &site;
%let site = %sysfunc(putn(&i,z2.));

data randomid_&site;
 set randomid;
 where site = &site;
run;
```

```
proc export data = randomid_&site
 outfile = 'c:\users\dgm\box sync\atxbio\Randomization Tables.xlsx'
 dbms = xlsx replace;
 sheet = "Site &site";
run;

title3 "Site &site";
ods rtf file = "c:\users\dgm\box sync\atxbio\site&site..rtf";
proc print data = randomid_&site label; run;
ods rtf close;
%end;
%mend to_excel;

%to_excel(site=49);
```