Statistical Analysis Plan: PTK0796-ABSI-16301

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABSSSI	acute bacterial skin and skin structure infection
ACM	all-cause mortality
AE	adverse event
BMI	body mass index
CE	clinically evaluable
CI	confidence interval
eCRF	electronic case report form
EMA	European Medicines Agency
EOT	end of treatment
FDA	Food and Drug Administration
I&D	Incision and drainage
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
IxRS	Interactive Response System
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
MIC	minimum inhibitory concentration
Micro-mITT	microbiological modified intent to treat
mITT	modified intent to treat
NDA	New Drug Application
NI	non-inferior
NSAIDs	nonsteroidal anti-inflammatory drugs
PD	pharmacodynamic
PK	pharmacokinetic
PO	orally
PR	interval from the P wave (atrial contraction or depolarization) to the onset of the Q wave in the measurement of electrical activity of the myocardium
PTE	post therapy evaluation
QTc	QT, corrected
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
TEAE	treatment emergent adverse event
US	United States

3 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the protocol PTK0796-ABSI-16301, "A Phase 3 Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of Oral Omadacycline to Oral Linezolid for Treating Adult Subjects with Acute Bacterial Skin and Skin Structure Infection (ABSSSI)." The statistical plan described is an *a priori* plan and no unblinded analysis prior to the preparation of this plan has been conducted. This SAP summarizes the study design and objectives, and provides details of the outcome definitions and statistical methods that will be used to analyze the data from protocol PTK0796-ABSI-16301.

The study has been designed to address both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory requirements; however, a separate SAP will be developed to address the different primary efficacy outcome and analyses for the EMA. While the EMA supports the assessment of clinical response by the Investigator at a Post Therapy Evaluation (PTE) visit (which is scheduled to occur 7 to 14 days after the last dose of test article) as the primary endpoint, the FDA guidelines require using an earlier primary endpoint (48 to 72 hours after the first dose of test article) based on reduction in lesion area.

4 TRIAL OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is to demonstrate that omadacycline administered orally for 7 to 14 days is non-inferior to linezolid administered orally for 7 to 14 days in the treatment of adult subjects with ABSSSI known or suspected to be due to Gram-positive pathogens.

4.2 Secondary Objectives

The secondary objectives are as follows:

- To evaluate the safety of omadacycline in the treatment of adult subjects with ABSSSI
- To evaluate the Clinical Response according to the identified causative pathogen
- To evaluate the pharmacokinetics (PK) of omadacycline in adult subjects with ABSSSI

5 STUDY DESIGN CONSIDERATIONS

5.1 Study Design

This is a randomized (1:1), double-blind, double-dummy, active comparator-controlled, Phase 3 study comparing omadacycline and linezolid for the treatment of adults with ABSSSI that is known or suspected to be due to a Gram-positive pathogen(s). Enrollment of subjects with major abscess may be up to 30% of randomized subjects. Enrollment of subjects who have received a single dose of an allowed short-acting antibiotic within the 72 hours prior to randomization will be limited to no more than 25% of randomized subjects. Subject randomization will be stratified across treatment groups by type of infection (wound infection, cellulitis/erysipelas or major abscess) and receipt of an allowed antibacterial therapy in the 72 hours prior to randomization.

Screening evaluations, with the exception of the blood culture, will be performed within 24 hours prior to randomization. The blood culture should be completed within the 24 hours prior to the first dose of test article. The day of the first dose of test article is defined as Day 1 and the day prior is Day -1; there is no Day 0. The study will have the following protocol-defined evaluations:

- Day 1, 2, 3, 7, 10 (A Day 10 visit should be conducted for subjects with treatment extending beyond 9 days, unless this coincides with the End of Treatment [EOT] visit.)
- EOT Visit: to be conducted on the calendar day of, or within 2 days following the last dose of any test article. If a subject withdraws prematurely or terminates participation in the study before completion, the EOT Visit should be conducted.
- PTE Visit: to be performed 7 to14 days after the subject's last day of study therapy.
- Final Follow-up assessment: Day 30 to 37 (after the first dose of test article).

A detailed Schedule of Study Procedures is provided in Appendix 1.

5.1.1 Sample Size

The study is designed to show NI in the primary efficacy outcome of Early Clinical Response at 48 to 72 hours following the first dose of test article in the modified Intent to Treat (mITT) population. An NI margin of 10% will be used for the analysis in the mITT population. The NI margin was based on an analysis of the historical data regarding the treatment effect of antibiotics in ABSSSI.

In the po study of tedizolid versus linezolid, the rates of Early Clinical Response (ECR) were 79% in both treatment arms in the ITT population[1]. Thus, an outcome rate of 79% in the mITT population was used for determination of the sample size. For the ECR primary efficacy endpoint, assuming an outcome rate of 79% for both treatment groups, NI margin of 10%, 90% power and a 1-sided alpha of 0.025, using the sample size determination method of Farrington and Manning[2], a total of 704 subjects are required.

The rates of clinical success based on the Investigator's Assessment at PTE were 86% in the ITT population and 95% in the CE population for linezolid, in the recent po clinical study in ABSSSI subjects[1]. To be conservative, outcome rates of 85% in the mITT and 90% in the CE population are used for the sample size determination. Assuming an 85% outcome rate in both treatment groups, NI margin of 10%, and a 1-sided alpha of 0.025, with a total of 704 subjects, there is more than 90% power to show NI for Investigator's Assessment of Clinical Response at PTE in the mITT population. With an evaluability rate of 80%, there will be 564 subjects in the CE population. Assuming a 90% outcome rate in both treatment groups, NI margin of 10% and a 1-sided alpha of 0.025, 564 subjects provides more than 90% power to show NI in the CE population.

Thus, a total of 704 subjects provide sufficient power for the primary efficacy analyses for both the FDA and EMA regulatory authorities. A summary of the sample size calculations and assumptions is provided in Table 1.

Table 1. Sample Size and Power Calculations

	Primary Efficacy Outcome FDA (Early Clinical Response)	Primary Efficacy Outcome EMA (Investigator's Assessment of Clinical Response at PTE)	
Population	mITT	mITT	CE
N	704	704	564
Outcome Rate	79%	85%	90%
Evaluability Rate	N/A	N/A	80%
Power	90%	96%	97%

CE = clinically evaluable; EMA = European Medicines Agency; FDA = United States Food and Drug Administration; mITT = modified intent-to-treat; N = number; N/A = not applicable; PTE = post therapy evaluation.

5.1.2 Randomization and Masking

All eligible subjects will be randomized via an Interactive Response System (IxRS) that assigns them to 1 of the treatment arms (in a 1:1 ratio). The site delegate will contact the IxRS (via phone or web) after confirming that the subject fulfills all the inclusion criteria and none of the exclusion criteria. The IxRS will assign a test article to the subject based on a computer-generated randomization schedule. The randomization will be a blocked randomization sequence stratified by type of infection (wound infection, cellulitis/erysipelas or major abscess) and receipt of an allowed antibacterial therapy in the 72 hours prior to randomization (yes or no). Subjects randomized into the study will be assigned the treatment corresponding to the next available number in the respective stratum of the computer-generated randomization schedule. The subject is considered randomized when the IxRS provides the test article assignment by providing a kit number (ie, completes a randomization transaction), regardless of whether the subject actually receives any medication. Enrollment of subjects with major abscess will be capped at 30% of the subjects randomized. Enrollment of subjects who have received an allowed antibacterial therapy in the 72 hours prior to randomization will be capped at 25% of the subjects randomized.

5.2 Efficacy Measures

5.2.1 Primary Efficacy Outcome

The primary outcome measure is Early Clinical Response at 48 to 72 hours (defined 46 hours to < 73 hours) after the first dose of test article in the mITT population. If more than one assessment of lesion size is done in the 46 to 72 hour time window, the latest will be used.

The primary outcome will be determined programmatically based on data recorded on the eCRF as follows:

Clinical Success will be defined as meeting all 3 of the following:

- The subject is alive
- The size of the primary lesion has been reduced ≥ 20% compared to Screening measurements, without receiving any rescue antibacterial therapy
- The subject does not meet any criteria for Clinical Failure or Indeterminate (see below for definitions)

Clinical Failure will be defined as meeting any of the criteria below:

- The size of the primary lesion has not been reduced by ≥ 20% compared to Screening measurements
- Investigator discontinued test article and indicated that the infection had responded inadequately such that alternative (rescue) antibacterial therapy was needed
- The subject received antibacterial therapy that may be effective for the infection under study for a different infection from the one under study up through the assessment of Early Clinical Response (ie, lesion size) or if no assessment was done in the 46 to 72 hour time window, up through 72 hours after the first dose of test article.
- The subject developed an AE that required discontinuation of test article prior to the Early Clinical Response assessment and alternative (rescue) antibacterial therapy was needed or if no assessment was done in the 46 to 72 hour time window, up through 72 hours after the first dose of test article.
- Death prior to Early Clinical Response assessment or if no assessment of Early Clinical Response (ie, lesion size) was done in the 46 to 72 hour time window, up to 72 hours after the first dose of test article.

Indeterminate The clinical response to test article could not be adequately inferred because:

- Subject was not seen for Early Clinical Response assessment because they withdrew consent, were lost to follow-up, or other specified reason
- Other specified reason

Subjects with missing data such that a response cannot be determined will be considered an indeterminate response. Since indeterminates are included in the denominator of the calculation of Early Clinical Success, these subjects are essentially Early Clinical Failures. For the mITT population, the proportion of mITT subjects with an Early Clinical Success is defined using the following formula:

$$\frac{\text{Number of subjects with an Early Clinical Success}}{\text{Number of subjects with an Early Clinical Failure + Number of subjects with a response of Indeterminate + Number of subjects with an Early Clinical Success}}$$

5.2.2 Secondary Efficacy Outcomes

5.2.2.1 Investigator's Assessment of Clinical Response

The investigator will make an assessment of Clinical Response at the EOT and PTE visits, based on the definitions below. The secondary efficacy outcome is the overall assessment of clinical response at PTE (derived from the investigator assessments at the EOT and PTE visits) in the mITT and CE-PTE populations as defined in Table 2.

5.2.2.1.1 EOT Visit

At the EOT visit (on the day of or within 2 days following the last dose of test article), the investigator will indicate the clinical status of the infection under study as detailed below.

Clinical Success at the EOT assessment will be defined as meeting the following:

- The subject is alive
- The infection is sufficiently resolved such that further antibacterial therapy is not needed. These subjects may have some residual changes related to infection requiring ancillary (ie, non-antibiotic) treatment, eg, bandages on a healing wound, debridement of uninfected tissue (ie, necrotic)

Clinical Failure will be defined as meeting any of the criteria below:

- Investigator discontinued test article and indicated that the infection had responded inadequately such that alternative (rescue) antibacterial therapy was needed
- The subject received antibacterial therapy that may be effective for the infection under study for a different infection from the one under study
- The subject developed an AE that required discontinuation of test article prior to completion of the planned test article regimen and alternative (rescue) antibacterial therapy was needed
- Unplanned major surgical intervention (ie, procedures that would not normally be performed at the bedside) for the infection under study
- The subject died before evaluation

- Other specified reason as indicated on the eCRF.

Indeterminate The clinical response to test article could not be adequately inferred:

- The subject was not seen for EOT assessment because they withdrew consent, were lost to follow-up, or other specified reason
- Other specified reason

5.2.2.1.2 PTE Visit

At the PTE Visit (7 to 14 days after the subject's last day of study therapy) the investigator will indicate one of the following outcomes relating to the primary infection under study:

Clinical Success at the Post Therapy Evaluation assessment will be defined as meeting the following:

- The subject is alive
- The infection is sufficiently resolved such that further antibacterial therapy is not needed. These subjects may have some residual changes related to infection requiring ancillary (ie, non-antibiotic) treatment, eg, bandages on a healing wound, debridement of uninfected tissue (ie, necrotic)

Clinical Failure will be defined as meeting any of the criteria below:

- The infection required additional treatment with alternative (rescue) antibacterial therapy
- The subject received antibacterial therapy between EOT and PTE that may be effective for the infection under study for a different infection from the one under study
- Unplanned major surgical intervention (ie, procedures that would not normally be performed at the bedside) for the infection under study between EOT and PTE
- The subject died before evaluation
- Other specified reason

Indeterminate The clinical response to test article could not be adequately inferred:

- The subject was not seen for PTE assessment because they withdrew consent, were lost to follow-up, or other specified reason
- Other specified reason

Overall Clinical Response at PTE (based on the investigator's assessment) is determined as follows (Table 2) from the investigator's assessments at the EOT and PTE Visits:

Table 2. Investigator's Assessment of Clinical Response

EOT Visit	PTE Visit	Overall Assessment of Clinical Response at PTE Visit
Success	Success	Success
Success	Failure	Failure
Success	Indeterminate	Indeterminate
Failure	Success	Failure
Failure	Failure	Failure
Failure	Indeterminate	Failure
Indeterminate	Success	Indeterminate
Indeterminate	Failure	Failure
Indeterminate	Indeterminate	Indeterminate

EOT = end of treatment; PTE = post-therapy evaluation.

For the mITT population, the proportion of mITT subjects with a Clinical Success is defined using the following formula (where the denominator adds to the total number of subjects in the mITT population):

$$\frac{\text{Number of subjects with Clinical Success}}{\text{(Number of subjects with Clinical Success + Number of subjects with a Clinical Failure + Number of subjects with an Indeterminate response)}}$$

By definition, subjects in the CE-EOT and CE-PTE populations cannot have an Indeterminate response. Thus, for the CE-EOT and CE-PTE populations, the proportion of subjects with a Clinical Success is defined using the following formula:

$$\frac{\text{Number of subjects with Clinical Success}}{\text{(Number of subjects with Clinical Success + Number of subjects with a Clinical Failure)}}$$

5.2.2.2 Microbiologic Outcomes

Microbiological response definitions for the evaluations performed at the EOT and PTE Visits and analyzed in the micro-mITT and ME populations are presented in Table 3 below. At the EOT and/or PTE visit, infection site specimen cultures and Gram stains should be obtained only for subjects who are clinical failures and require alternative antibacterial treatment for the infection under study.

If a subject has the same pathogen (ie, same genus and species) identified from both an ABSSSI and blood specimen, a microbiological response is determined for each of the pathogens. For tables summarizing microbiologic response for pathogens from the ABSSSI or blood specimen, if the same pathogen is isolated from both an ABSSSI and blood specimen, the worst response is summarized. The microbiologic response for the ABSSSI pathogen is based on the pathogen isolated from the EOT or PTE specimen, if a specimen was collected. The microbiologic response for the blood pathogen is based on the blood sample collected at EOT or PTE, or if a sample was not collected at the post-baseline visit, the blood sample collected prior to and closest to the visit.

Table 3. Per-Pathogen Microbiological Response Definitions at the EOT and PTE Visits

Term	Definition
Eradication	Absence of original baseline pathogen
Presumed Eradication	No source specimen to culture in a subject assessed with a clinical success by the Investigator
Persistence	Continued presence of the original baseline pathogen
Presumed Persistence	No source specimen to culture in a subject assessed with a clinical failure by the Investigator
Indeterminate	The subject's clinical response is indeterminate or other circumstance that precludes a microbiological evaluation

EOT = end of treatment; PTE = post-therapy evaluation.

Microbiological outcomes are further categorized as favorable, unfavorable and indeterminate. Favorable microbiological outcomes are defined as eradication or presumed eradication. Unfavorable microbiological outcomes are defined as persistence or presumed persistence. Microbiological response will be derived using electronic microbiology data from the central laboratory (or local laboratory if central data are not available) and from pathogen determination provided by the sponsor for each baseline isolate.

Overall microbiological response at PTE is determined as follows (Table 4) from the microbiological responses at the EOT and PTE Visits:

Table 4. Per-Pathogen Microbiologic Response

EOT Visit	PTE Visit	Overall Microbiologic Response at PTE
Favorable	Favorable	Favorable
Favorable	Unfavorable	Unfavorable
Favorable	Indeterminate	Indeterminate
Unfavorable	Favorable	Unfavorable
Unfavorable	Unfavorable	Unfavorable
Unfavorable	Indeterminate	Unfavorable
Indeterminate	Favorable	Indeterminate
Indeterminate	Unfavorable	Unfavorable
Indeterminate	Indeterminate	Indeterminate

Note: Favorable is defined as eradication or presumed eradication. Unfavorable is defined as persistence or presumed persistence.
EOT = end of treatment; PTE = post-therapy evaluation.

Per-subject responses will be based on per-pathogen outcomes. To have an overall per-subject favorable microbiologic response, the outcome for each baseline pathogen must be favorable (eradicated or presumed eradicated). If the outcome for any pathogen is unfavorable (persistence or presumed persistence), the subject will be considered to have an unfavorable per-subject microbiologic response. Subjects with an indeterminate response for all pathogens will be considered to have an indeterminate per-subject microbiologic response. If the same pathogen is isolated from both the blood and the ABSSSI site culture, the worst outcome will be used to determine per-subject microbiologic response. Superinfections will not be considered in the microbiological response. Microbiological response from worst to best are as follows: persistence, presumed persistence, indeterminate, presumed eradication and eradication.

The overall per-subject microbiologic response at PTE is determined from the per-subject microbiologic responses at the EOT and PTE Visits as follows (Table 5):

Table 5. Per-Subject Microbiologic Response

EOT Visit	PTE Visit	Overall Microbiologic Response at PTE
Favorable	Favorable • Eradication • Presumed Eradication	Favorable • Eradication • Presumed Eradication
Favorable	Unfavorable • Persistence • Presumed Persistence	Unfavorable • Persistence • Presumed Persistence
Favorable	Indeterminate	Indeterminate
Unfavorable • Persistence • Presumed Persistence	Favorable	Unfavorable • Persistence • Presumed Persistence
Unfavorable • Persistence • Presumed Persistence	Unfavorable • Persistence • Presumed Persistence	Unfavorable • Persistence • Presumed Persistence
Unfavorable • Persistence • Presumed Persistence	Indeterminate	Unfavorable • Persistence • Presumed Persistence
Indeterminate	Favorable	Indeterminate
Indeterminate	Unfavorable • Persistence • Presumed Persistence	Unfavorable • Persistence • Presumed Persistence
Indeterminate	Indeterminate	Indeterminate

Note: Favorable is defined as eradication or presumed eradication. Unfavorable is defined as persistence or presumed persistence.
EOT = end of treatment; PTE = post-therapy evaluation.

For the microbiological modified intent to treat (micro-mITT) population, the proportion of subjects with a favorable microbiological response is defined using the following formula (where the denominator adds to the total number of subjects in the micro-mITT population):

$$\frac{\text{Number of subjects with eradication + Number of subjects with presumed eradication}}{\text{(Number of subjects with eradication + Number of subjects with presumed eradication + Number of subjects with persistence + Number of subjects with presumed persistence + Number of subjects with indeterminate response)}}$$

By definition, the microbiological evaluable (ME) populations (ME-EOT and ME-PTE) must have sufficient information to determine the outcome and thus, excludes subjects with indeterminate responses. For the ME analysis set, the proportion of subjects with a microbiological response is defined using the following formula:

$$\frac{\text{Number of subjects with eradication + Number of subjects with presumed eradication}}{\text{(Number of subjects with eradication + Number of subjects with presumed eradication + Number of subjects with persistence + Number of subjects with presumed persistence)}}$$

Microbiological response definitions of superinfection and new infection are presented in Table 6 below:

Table 6. Microbiological Response Definitions: Superinfection or New Infection

Term	Definition
Superinfection	Isolation of a non-baseline ABSSSI pathogen from the primary ABSSSI site or blood while the subject is on test article (ie, during test article administration, Day 1 to EOT) and the subject has worsening or new signs or symptoms of the primary ABSSSI (ie, the subject is deemed a clinical failure by the investigator)
New infection	Isolation of a non-baseline ABSSSI pathogen from a post-treatment (ie, after EOT) culture from the primary ABSSSI site or blood in a subject with worsening or new signs or symptoms of the primary ABSSSI (ie, the subject is deemed a clinical failure by the investigator)

ABSSSI = acute bacterial skin and skin structure infection.

For subjects with multiple microbiological samples taken either during test article administration (for determination of superinfection) or after test article administration (for determination of new infection) all cultures will be used in the analysis.

5.3 Safety Measures

The safety parameters include AEs, clinical laboratory evaluations, vital signs, and ECG findings. AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 17.1 or higher to the System Organ Class and Preferred Term levels.

5.4 Pharmacokinetic Parameters

The concentration of omadacycline will be obtained from plasma samples. Refer to the pharmacokinetic analysis plan for further details.

6 STUDY POPULATIONS

6.1 Analysis Populations

6.1.1 Intent-to-Treat (ITT) Population

The ITT population will consist of all randomized subjects regardless of whether or not the subject received test article. A subject is considered randomized when the IxRS provides the test article assignment by providing the kit number (ie, completes a randomization transaction).

6.1.2 Safety Population

The Safety population will consist of all randomized subjects who receive test article. All safety analyses will be conducted in this analysis set.

6.1.3 Modified Intent-to-Treat (mITT) Population

The mITT population will consist of all randomized subjects without a baseline sole Gram-negative ABSSSI pathogen. Pathogen determination is described in Section 6.1.4.

6.1.4 Microbiological Modified Intent-to-Treat (micro-mITT) Population

The micro-mITT population will consist of all subjects in the mITT population who have at least one Gram-positive causative bacterial pathogen identified from a blood culture or from a culture of a microbiological sample obtained from the primary ABSSSI site at baseline using a valid sampling technique. Pathogen determination is based on the genus and species identification from the central laboratory. If the local laboratory grows an acceptable pathogen but the central laboratory is not able to grow the isolate, if isolates are lost during transportation or storage, or there are major discrepancies between the local and central laboratory in the identification of species, the central laboratory or other Sponsor designee will request that the local laboratory resend the isolate. If the central laboratory cannot determine the genus and species of the isolate for any reason, the local laboratory determination of genus and species will be used for pathogen identification. The central laboratory identification of genus and species is used for analysis unless no central determination exists in which case the local laboratory determination is used. If the central lab does not speciate the pathogen but the local/regional lab does speciate the pathogen, the Sponsor will make the final determination as to which pathogen identification is used for analysis.

An acceptable ABSSSI site specimen obtained via a valid sampling technique is defined as one obtained from a biopsy of involved cutaneous or subcutaneous tissue preferably from the advancing margin of the lesion, debrided tissue, tissue scraping (using curette or scalpel), needle aspirate of involved, nonpurulent cutaneous or subcutaneous tissue, pus or infected tissue collected during an incision and drainage procedure, pus aspirated into a syringe or a deep swab of purulent material (only if collected from infected tissue that has been incised or is draining). Surface swabs of wounds, inflamed skin or drainage (including purulent material) are not considered valid sampling techniques. If more than one baseline ABSSSI site sample was obtained using a valid sampling technique or more than one baseline blood sample was obtained, isolates from all samples will be reviewed for pathogen determination.

For subjects that have ABSSSI and blood specimens collected per protocol, baseline is defined as either Day –1 or 1. For subjects with cellulitis/erysipelas, if no acceptable baseline infectious material has been obtained or if no pathogens have been identified from the baseline sample, a Day 2 or 3 microbiological sample can be used as baseline if the sample is considered acceptable. If acceptable ABSSSI site and/or blood samples are obtained on both Study Days -1 and 1, all isolates will be reviewed for pathogen determination.

The 3 categories of pathogen classification are as follows:

1. Always a pathogen: If isolated from the culture of the ABSSSI, the following are always considered a pathogen:
   - Monomicrobial infections caused by
     - *Staphylococcus aureus* - isolates will be reviewed by oxacillin susceptibility results (methicillin resistant - MRSA and methicillin susceptible - MSSA) and MRSA and MSSA will be considered distinct pathogens.
     - Group A, B, C and G β–hemolytic streptococci (ie, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus pyogenes*, etc.)
     - *Streptococcus anginosus* group (eg, *Streptococcus anginosus, Streptococcus intermedius, Streptococcus constellatus*)
     - *Enterococcus faecalis* - isolates will be reviewed by vancomycin susceptibility results (vancomycin resistant *Enterococcus faecalis* and vancomycin susceptible *Enterococcus faecalis*) and these will be considered distinct pathogens.
     - *Enterococcus faecium* - isolates will be reviewed by vancomycin susceptibility results (vancomycin resistant *Enterococcus faecium* and vancomycin susceptible *Enterococcus faecium*) and these will be considered distinct pathogens.
     - *Staphylococcus lugdunensis*
     - Gram positive anaerobes isolated from a major abscess or wound infection
   - Polymicrobial infection consisting of any combination of *Staphylococcus aureus*, Group A, B, C and G β –hemolytic streptococci and *Streptococcus anginosus* group
2. Never a pathogen: If isolated from the culture of the ABSSSI, the following are never a pathogen:
   - *Corynebacterium* spp.
   - *Bacillus* spp.
   - *Diphtheroids*
   - *Micrococcus* spp.
   - *Propionibacterium* spp.
   - *Actinomyces* spp.
   - *Actinobaculum* spp.
   - *Porphyromonas* spp.

- All coagulase-negative staphylococci with the exception of *S. lugdunensis* (eg, *S. capitis, S. caprae, S. cohnii, S. condiment, S. epidermidis, S. haemolyticus, S. hominis, S. saprophyticus, S. sciuri, S. simulans, S. warneri, S. xylosus*)
- Gram positive anaerobes isolated from cellulitis/erysipelas
- *Candida* spp., *Aspergillu*s spp., or other fungi

3. Case-by case review: The following organisms will be assessed on a case-by-case basis via manual review by the Sponsor. If needed, subject clinical (eg, type of infection, type of specimen, subject underlying conditions, etc.) and microbiological information (eg, amount of culture growth, etc.) will be used to assist in determining if the isolate is a pathogen.
   - Monomicrobial infection with an organism not listed in #1 or #2 above
   - Polymicrobial infections (infections with ≥ 2 pathogens) will be reviewed on a case-by-case basis, except as noted above for always a pathogen.
   - All organisms isolated from a blood culture
   - All Gram-negative organisms

6.1.5 Clinically Evaluable (CE) Populations

Two CE analysis sets will be defined; the CE-EOT and the CE-PTE. To be included in the CE-EOT and the CE-PTE populations, subjects must be in the mITT population. Subjects will be *included* in or *excluded* from the CE analysis sets based on the additional criteria listed below.

6.1.5.1 Diagnosis of ABSSSI

To be included in the CE-EOT and CE-PTE populations, subjects must meet the following protocol defined inclusion criteria that describe the ABSSSI:

Inclusion Criterion 3: Has a qualifying skin and skin structure infection. All qualifying lesions must be greater than or equal to 75 cm^2 in total surface area of contiguous involved tissue, calculated as the product of the maximum length (head-to-toe) multiplied by the maximum width (measured perpendicular to length) as measured by the investigator using a wound ruler. Involved tissue is defined as tissue exhibiting clear evidence of one or more of the following: erythema, edema, or induration.

The classification of qualifying infections is shown below:

a. Wound infection – an infection characterized by purulent drainage from a wound with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound.
b. Cellulitis/erysipelas – a diffuse skin infection characterized by spreading areas of erythema, edema, and/or induration.
c. Major abscess – an infection characterized by a collection of pus within the dermis or deeper that is accompanied by erythema, edema and/or induration extending at least 5 cm of in the shortest distance from the peripheral margin of the abscess.

Inclusion Criterion 4: Has evidence of a systemic inflammatory response within the 24 hours prior to randomization, as indicated by ONE of the following:

a. Elevated white blood cell (WBC) count (greater or equal to 10,000 cells/mm^3) or leukopenia (less than or equal to 4,000 cells/mm^3)
b. Elevated immature neutrophils (greater than or equal to 15% band forms) regardless of total peripheral WBC count
c. Lymphatic involvement: lymphangitis or lymphadenopathy that is proximal to and in a location that suggests drainage from the qualifying infection
d. Fever or hypothermia documented by the investigator (temperature greater than 38.0°C [100.4°F] or less than 36.0°C [95.5°F])

6.1.5.2 Prior Antibiotic Therapy

Subjects will be excluded from the CE populations if they meet either of the prior antibiotic exclusion criteria:

Exclusion Criterion 1: Has received 1 or more doses of a potentially effective systemic antibacterial treatment within the 72-hour period prior to randomization (a subject will be considered to have received a potentially effective systemic antibacterial treatment if the pathogen identified as causing the infection is shown to be susceptible to the antibacterial treatment given or, in the circumstance where a pathogen is not identified, if the antibacterial agent is approved for treatment of skin infections or is known to have activity against any of the leading Gram-positive causes of ABSSSI (eg, *Staphylococcus aureus*, *Streptococcus* species [spp.], *Enterococcus* spp.]). EXCEPTION: Subjects may be eligible despite prior antibacterial therapy if they have been treated with a single dose of a short-acting, non-oxazolidinone antibacterial (ie, an antibacterial whose standard dosing regimen is more frequent than once per day, see list in Appendix 1 of the protocol).

Exclusion Criterion 2: Has, for any reason, used a topical antibacterial agent(s) with specific antibacterial activity (eg, mupirocin, retapamulin, fusidic acid) continuously within the 72-hour period prior to first dose of test article, if applied to the skin for greater than or equal to 72 hours.

6.1.5.3 Concomitant Antibiotic Therapy

Subjects who receive any systemic concomitant antibiotic therapy from the first dose of test article through the EOT visit and through the PTE visit with a spectrum of activity against the known or potential Gram-positive infecting pathogen(s) responsible for the infection under study will be excluded from the CE-EOT and CE-PTE populations, respectively, unless the subject receives the antibiotic therapy for treatment of the ABSSSI due to insufficient therapeutic effect of the test article.

Subjects who receive a systemic concomitant antibiotic that is not effective against the Gram-positive baseline pathogen, or if no Gram-positive pathogen is isolated and the antibiotic does not have Gram-positive activity, will be included in the CE-EOT and CE-PTE populations.

In addition, subjects who have any topical antibacterial agent applied to the infection site (except for antibiotic/antiseptic-coated dressing applied to the clean postsurgical wound) with a spectrum

that is active against the known or potential infecting pathogen(s) responsible for the infection under study from the first dose of test article through the EOT or PTE visits, will be excluded from the CE-EOT and CE-PTE populations, respectively.

Antimicrobials that will not interfere with the course of the ABSSSI are allowed and do not affect inclusion in the CE populations, eg, metronidazole, norfloxacin, nalidixic acid, pipemedic acid, oral vancomycin, antifungals, antivirals or topical antibiotics used for decontamination or in places other than the primary lesion.

6.1.5.4 Concomitant Surgical Procedures

Subjects who receive an unplanned major surgical procedure for the infection under study (ie, procedures that would not normally be performed at the bedside, such as amputation or major incision and drainage performed in an operating room) will be defined as a clinical failure for the clinical response at the EOT and PTE Visits and thus, will be included in the CE populations.

Minor bedside procedures such as debridement, aspiration puncture, excision with or without skin grafting and wound cleaning/lavage will generally be acceptable and will not exclude a subject from the CE populations. All other surgical procedures performed after the first dose of test article will be reviewed by the Sponsor to determine whether the procedure potentially confounds the outcome and whether the subject should be excluded from either the CE-EOT or CE-PTE populations.

6.1.5.5 Test Article Therapy

Subjects must meet all of the following to be included in the CE populations:

- Received test article and the correct test article based on the randomization assignment
- Study personnel involved in the assessment of efficacy remained blinded to study treatment, unless a treatment limiting adverse event occurred which required emergency unblinding.
- Subject was at least 80% compliant with the dosing regimen.
- Evaluable failure: The subject received at least 2 doses of active test article (omadacycline group) or at least 4 doses of active test article (linezolid group) and the investigator classifies the subject as a Clinical Failure at the EOT Visit (CE-EOT population) or the overall Clinical Response (based on the investigator's assessment) at the PTE Visit (CE-PTE population) is Clinical Failure.
- Evaluable success: The subject received at least 3 doses of active test article (omadacycline group) at least 6 doses of active test article (linezolid group) and the investigator classifies the subject as a Clinical Success at the EOT Visit (CE-EOT population) or the overall Clinical Response (based on the investigator's assessment) at the PTE Visit (CE-PTE population) is Clinical Success.

6.1.5.6 Clinical Outcome Assessment

Subjects must meet the following to be included in the CE populations:

- For the CE-EOT population:
  - Completed the investigator's assessment of clinical response (ie, was not deemed an indeterminate outcome) at the EOT visit, and
  - The EOT visit occurred on the day of, or within 2 days following the last dose of test article.
- For the CE-PTE population:
  - The overall Clinical Response (based on the investigator's assessment) at the PTE Visit is not Indeterminate.
  - The PTE Visit occurred 7 to 14 days after the last dose of test article, unless the subject was considered to be a Clinical Failure based on the investigator's assessment at the EOT visit.

6.1.5.7 Baseline Medical Events

Subjects will be excluded from the CE populations if the investigator has documented in the eCRF that they meet any one of the following protocol-defined exclusion criteria at baseline (ie, prior to randomization):

Exclusion Criterion 3: Infections where the outcome is strongly influenced by factors other than protocol-defined treatment and procedures, that require antibacterial treatment for greater than 14 days, are associated with chronic skin lesions that may obscure determination of response even after successful bacterial eradication has been achieved, or are suspected or known to be caused by a pathogen resistant to either test article, eg:

- Chronic (persistently present greater than 3 months) lesions, ulcers or wounds (eg, cellulitis contiguous with a diabetic foot ulcer)
- association with chronic dermatitis or any other chronic inflammatory skin lesion (eg, psoriasis, eczema)
- burns
- peri-rectal abscess (eg, buttock or perineal lesion likely to communicate with the rectum) or perineal infection
- infected decubitus (pressure) ulcers
- necrotizing fasciitis (infections with rapidly progressive destruction of tissue at or below the fascia)
- life-threatening infections, ie, require emergency surgery for the treatment (eg, progressive gangrene)
- infections in an area requiring surgery that in and of itself would cure the infection or remove the infected site (eg, amputation for vascular insufficiency)

- infections associated with severe vascular insufficiency (eg, peripheral vascular disease) or acute occlusion expected to require immediate revascularization
- infections associated with acute compartment syndrome expected to require extensive surgery to provide decompression
- infections accompanied by confirmed or suspected contiguous bone or joint infection (eg, osteomyelitis, septic arthritis, bursitis)
- bacteremic infections associated with an intravascular foreign body
- infections accompanied by another confirmed or suspected infection requiring systemic antibiotic therapy (eg, endocarditis, other endovascular infection, meningitis, visceral abscess, intra-abdominal infection, pneumonia, urinary tract infection)
- human or animal bites (infections associated with insect bites are NOT excluded)
- myonecrosis
- complicated by an immune deficiency in the subject (eg, ecthyma gangrenosum in a neutropenic subject)
- infections associated with the presence of a foreign body (eg, wood, metal, plastic, etc.) if the foreign body cannot be removed within 24 hours of first dose of test article

Exclusion 4: Inability to tolerate oral medication (eg, nausea, vomiting diarrhea or any other condition that might impair ingestion or absorption of oral medication)

Exclusion 19: Has been previously treated with omadacycline or previously enrolled in this study.

6.1.6 Microbiologically Evaluable (ME) Populations

The ME-EOT and ME-PTE populations will consist of all subjects in both the micro-mITT and the CE-EOT and CE-PTE populations, respectively.

6.2 Evaluability Review Team

6.2.1 Membership and Responsibilities

The Evaluability Review Team (ERT) will review both clinical and microbiological data for determination of criteria used to assess inclusion in the analysis populations and for determination of baseline and post-baseline pathogens. ERT members will be blinded to treatment assignment and will review the data concurrent with the conduct of the study. The ERT will be conducted in accordance with the ERT process documents.

6.2.2 Process for Determining Inclusion in Populations

Inclusion into the ITT and Safety populations will be determined programmatically from the eCRF data. Inclusion into the CE populations will be determined programmatically from the

eCRF data and the manual review conducted by the ERT. The ERT may review subject data to confirm that population criteria are satisfied.

Inclusion into the mITT and micro-mITT population will be determined programmatically by incorporating the outcome of the review of the isolates by the ERT. The ERT will determine whether each isolate (baseline and post-baseline) is considered a pathogen based on a review of information from baseline samples including infection type, type of specimen, and local and central laboratory genus and species identification. Inclusion into the ME populations will be determined programmatically.

Review of data, Sponsor determination of evaluability, and final subject population classification will be performed in a blinded manner prior to database lock and unblinding with the exception of those criteria requiring the subject's actual treatment assignment (for example, the requirement for the subject to have received the correct test article per the randomization assignment). For the criteria requiring the subject's actual treatment assignment, population determination will be completed programmatically after unblinding.

6.3 Subgroups

Analyses of Early Clinical Response and the overall assessment of Clinical Response at the PTE Visit (based on the investigator's assessment) will be conducted (as described in Section 10.6) for subgroups defined by the randomization stratification factors: infection type (cellulitis/erysipelas, wound infection and major abscess) and receipt of an allowed antibacterial therapy in the 72 hours prior to randomization (yes or no). Analyses of Early Clinical Response will also be conducted in the following subgroups: clinical site (sites that enroll less than 10 subjects per group will be grouped together), bacteremic subjects, subjects meeting the systemic inflammatory response syndrome (SIRS) criteria at baseline, size of lesion (≤ 300 cm^2, > 300 to 600 cm^2, > 600 to 1000 cm^2, and > 1000 cm^2), receipt of a nonsteroidal anti-inflammatory drug (NSAID) from the first dose of test article through to the assessment of Early Clinical Response, receipt of an operative incision and drainage (I&D) from the first dose of test article through to the assessment of Early Clinical Response and IV drug use vs no IV drug use . SIRS is defined as having 2 or more of the following criteria: temperature $< 36^o$ C or $> 38^o$ C, heart rate > 90 bpm, respiratory rate > 20 bpm, or WBC count < 4000 cells/mm^3 or > 12,000 cells/mm^3 or > 10% bands.

Exploratory analyses in other subgroups may also be conducted.

7 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

There are no changes to the analyses as detailed in the protocol.

8 OVERALL STATISTICAL CONSIDERATIONS

8.1 General Conventions

The following general comments apply to all statistical analyses and data presentations:

- Summaries will include frequency and percentages for categorical data; frequency and median for ordinal data; and frequency, mean, standard deviation, and median, minimum and maximum for quantitative data.
- Duration variables will be calculated using the general formula (end date − start date) + 1.
- Change from baseline will be calculated for each subject at the specified time point as the value at the specified time point minus the baseline value.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (eg, a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as '< 10' or '≤ 5' will be treated as '10' or '5' respectively, and a value such as '> 100' will be treated as '100.' However, the actual values as reported in the database will be presented in data listings. Data will be reviewed on an ongoing basis in a blinded manner to assess the frequency of occurrence of laboratory parameters reported as a character string.
- Individual subject listings of all data represented on the eCRFs will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety parameters.
- Version 9.3 (or higher) of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

8.2 Baseline Definition

In general, baseline is defined as the value closest to but prior to the initiation of test article administration. If no test article is received, baseline is defined as the value closest to but prior to randomization.

For pathogen determination, baseline is defined as either Day –1 or 1. For subjects with cellulitis/erysipelas, if no acceptable baseline infectious material has been obtained or if no pathogens have been identified from the baseline sample, a Day 2 or 3 microbiological sample can be used as baseline if the sample is considered acceptable. If no test article is received, for pathogen determination, study day is defined based on date of randomization.

For analyses of vital signs and ECGs, if no value is available prior to the initiation of test article administration, a value within 2 hours after initiation of test article administration can be used as baseline.

8.3 Handling of Missing Data

Missing data will be handled as outlined below:

- All missing and partial dates for adverse events or for medications received after randomization will be queried for a value. If no value can be obtained, substitutions will be made as detailed in Appendix 3. These substitutions will be used in calculations; however, the actual value recorded on the eCRF will be used in all listings.
- Missing start and stop times for prior and concomitant antibiotics will be queried for a value. If no value can be obtained but the site indicates the antibiotic was received (onset time) prior to the first dose of test article, 00:01 will be used for the onset time. If the site also indicates that the end time was prior to the first dose of test article, 00:01 will be used for end time. The actual value (blank) will be recorded on the eCRF and will be used in the listings.
- Missing times for lesion measurements will be queried for a value. If minutes are not available, the time will be recorded to the closest hour.
- If the time of the outpatient dose of test article on Day 1 is missing, it will be imputed to 23:59.
- If no value can be obtained for all other times for events and assessments occurring after randomization, the time will not be imputed but will remain missing.
- The severity and causality assessment for adverse events cannot be missing. Missing data will be queried for a value.

For clinical and microbiological response, missing data will be handled as follows:

- For the primary outcome measure (Early Clinical Response at 48 to 72 hours):
  - The subject will be considered to have missing data if there is no lesion size measurement (either length or width) at either baseline or 46 to 72 hours after the first dose of test article. Subjects with missing data will be defined as an Indeterminate response which is essentially a Clinical Failure for the primary analysis (mITT and ITT populations).
  - If the time of administration of the first dose of test article is missing, the subject will be defined as an Indeterminate response which is essentially a Clinical Failure for the primary analysis (mITT and ITT populations).
- For the secondary outcome measures (investigator's assessment of Clinical Response at the EOT and PTE Visits):
  - Subjects will be defined as an Indeterminate if the investigator cannot determine whether the subject is a Clinical Success or Failure at the EOT or PTE Visits or the subject has a missing response. By definition, subjects with an Indeterminate response are included in the denominator for analyses in the mITT and micro-mITT populations, and thus, are considered Clinical Failures. Subjects with an Indeterminate response are excluded from the CE-EOT, CE-PTE, ME-EOT and ME-PTE populations.

- For microbiologic response:
  - If no source specimen is obtained and the subject has an investigator's assessment of Clinical Response, the per-pathogen microbiological response is based on the investigator's assessment of Clinical Response (ie, the response is a presumed response). A per-pathogen microbiological response at the EOT Visit or PTE Visit will be considered Indeterminate only if the Clinical Response at EOT or PTE is also Indeterminate.
- Missing values for other individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.
- Where individual data points are missing, categorical data will be summarized based on reduced denominators (ie, only subjects with available data will be included in the denominators).

8.4 Interim Analysis

An interim analysis to assess efficacy or safety is not planned.

8.5 Pooling Strategy for Study Sites

Data will be pooled across sites for all efficacy and safety analyses. An analysis of the primary (Early Clinical Response) and secondary (Investigator assessment of clinical response) efficacy outcomes will be conducted by site. Sites that enroll less than 10 subjects per arm will be pooled together for the by site analysis.

8.6 Visit Windows/Unscheduled Visits

For the primary efficacy outcome, if more than one assessment of the lesion size is done in the 46-72 hour window, the latest will be used. For secondary and additional efficacy outcomes, the data collected at the EOT and PTE Visits, regardless of when these occur will be utilized in the analysis in the mITT population. The CE and ME populations exclude subjects with a visit occurring outside the window allowed per protocol.

For each safety outcome, analyses will utilize assessments occurring during the scheduled visit windows (provided in Table 7). Thus, if a subject has a visit outside the scheduled visit window, for example, a PTE Visit occurred 20 days after the subject's last day of therapy, the assessment will not be summarized with the PTE Visit but will be considered an unscheduled assessment. If a subject does not have an assessment at a scheduled visit and an unscheduled assessment was taken within the window for the time point (for example, 7 to 14 days after the subject's last day of therapy for PTE), these assessments will be summarized in the by time point analyses. If more than one measurement is taken during the visit window, the value taken on the scheduled visit will be utilized or if no scheduled visit was done, the first (earliest) measurement in the visit window will be used. If more than one measurement is taken on the same day, the assessment closest to the start of the dose will be used for on treatment values and the last measurement on the day will be used for post-treatment values. For worst overall post-baseline analyses, all assessments including those obtained from unscheduled visits will be included.

Table 7. Scheduled Study Visits

Study Visit	Study Day	Notes
Baseline	Day -1 or Day 1	Except where indicated, last measurement prior to the first dose of test article. Screening assessments are to be taken within 24 hours prior to the first dose of test article. If no test article is taken, the date and time of randomization is used in place of the first dose of test article.
On Treatment (note: analysis visit will be each Study Day)	Day 1, Day 2, Day 3, Day 7, Day 10	The Day 3 visit is to occur within 46 to 72 hours after the first dose of study drug and thus, may occur on Study Day 4. A Day 10 visit is will be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the EOT Visit.
EOT		Within 2 days following the last dose of test article
PTE		7 to 14 days after the subject's last day of therapy
Final Follow-up (FU)	Day 30 to 37	30 to 37 days after the start of the first dose of test article

Study Day is calculated relative to the first dose of test article (Day 1); there is no Day 0 – the day prior to the first dose of test article is Day -1. If no test article is taken, study day is calculated relative to the date of randomization.

9 STATISTICAL ANALYSIS METHODS

9.1 Subject Disposition

The number of Screen Failures and reason for screen failure will be presented overall. A listing, grouped by stratum, will be provided that indicates the subject's date and time of randomization, randomized treatment assignment, randomization number, kit number(s), block number, randomized infection type, and prior antibiotic stratum (receipt of an allowed antibacterial therapy in the 72 hours prior to randomization - yes or no).

The number of subjects included in each of the analysis populations (ie, ITT, Safety, mITT, micro-mITT, CE-EOT, CE-PTE, ME-EOT and ME-PTE) will be summarized by treatment group. A table will summarize the reasons for exclusion from each population and a listing will be provided that indicates each subject's inclusion in/exclusion from the populations and the reason for exclusion from each of the populations.

A listing will be provided of randomized subjects who did not meet all inclusion/exclusion criteria, and which criteria were not met. The number and percentage of subjects completing the study (defined as receiving at least one dose of test article and returning for all of the EOT, PTE and FU visits), not completing the study, missing each of the EOT and PTE Visits, and prematurely discontinuing from test article will be presented for each treatment group and overall for the ITT, mITT, and CE-PTE populations (by definition, a subject in the CE-PTE population cannot have missed the PTE Visit, unless the subject was a clinical failure at the EOT Visit). Reasons for premature discontinuation of test article, not completing the study, and for missing each of the visits, as recorded on the eCRF will be summarized (number and percentage) by treatment group. Percentages of subjects discontinued from test article and not completing the study will be compared between treatment groups using Fisher's exact test. A listing of all subjects who prematurely discontinued from test article or not completing the study will be presented, and the primary reason for discontinuation of test article or not completing the study will be provided.

9.2 Demographics and Baseline Characteristics

Except where indicated, demographic data and baseline characteristics will be presented by treatment group for the Safety, mITT, micro-mITT, and CE-PTE populations. A table will present the subject demographics (eg, gender, age, ethnicity, and race) and baseline characteristics (height, weight, BMI, and renal function). Age will be calculated from the date of birth to the informed consent date and will be summarized as a continuous variable and categorized (18 to 45 years, > 45 to 65 years, > 65 to 75 years and > 75 years). Renal function will be categorized as normal (creatinine clearance [CrCl] > 80 mL/min), mild renal impairment (CrCl > 50 to 80 mL/min), moderate renal impairment (CrCl 30 to 50 mL/min) and severe renal impairment (CrCl < 30 mL/min). Creatinine clearance will be calculated from the local laboratory data and will be determined from the Cockcroft-Gault equation:

$$\frac{(140\text{-age[yrs]})*\text{weight [kg]}*(Z)}{\text{Cr [mg/dL]} * 72}$$

Z = 1.0, if Male
Z = 0.85, if Female

Differences between treatment groups will be analyzed using Fisher's exact test for dichotomous variables (gender, ethnicity, and race) and the Wilcoxon Rank Sum test for continuous variables (age, height, weight, and BMI).

The number and percentage of subjects with reported ABSSSI relevant medical history (relevant surgical procedure that resulted in the primary infection, recent trauma that resulted in the primary infection, iv drug abuse, prior ABSSSI, association of ABSSSI with chronic skin lesions, concurrent secondary ABSSSI lesions, diabetes mellitus [based on the MedDRA higher level term "Diabetes mellitus (incl subtypes)"], hepatitis C [based on the MedDRA preferred terms of "Hepatitis C" and/or "Chronic Hepatitis C"], infection result of vascular insufficiency or edema, and peripheral artery disease) will be summarized by treatment group for the mITT and CE-PTE populations. Differences between treatment groups in the percent of subjects with each relevant medical history will be determined using Fisher's exact test. Other medical and surgical history will be coded using MedDRA and summarized based on MedDRA system organ class and treatment group for the mITT and Safety populations. The number and percentage of subjects with a history of diabetes mellitus and hepatitis C will be presented by treatment group in the Safety population.

Listings will be provided of those subjects who were randomized to the wrong ABSSSI type of infection stratum and wrong prior antibiotic stratum. The type of infection listing will provide the subject ID, treatment group, randomized type of infection and actual (as recorded on the eCRF) type of infection. The prior antibiotic listing will provide the subject ID, treatment group, randomization date and time, randomized prior antibiotic stratum, preferred term of prior antibiotic, start and stop date/time of prior antibiotic, hours prior to randomization, dose and frequency of the antibiotic.

Descriptive statistics of the primary infection site will be provided for the mITT and CE-PTE populations. These include type of ABSSSI infection (cellulitis/erysipelas, major abscess, wound infection) and anatomical site (categorized as scalp, neck, face, chest, abdomen, back, groin, hand, foot, shoulder, buttock, axillary, arm, leg, elbow and knee). Lesion measurements (length, width and area of erythema, edema and/or induration, and for subjects with wounds and abscesses, the shortest measurement from peripheral margin), local signs and symptoms (tenderness, edema, erythema, induration, and drainage [none, serous/serosanguineous, seropurulent, and purulent]), and systemic signs (lymphadenopathy proximal to primary lesion site, presence of lymphangitis proximal to primary lesion site, WBC count $\geq$ 10,000 cells/mm^3 or $\leq$ 4000 cells/mm^3, $\geq$ 15% immature neutrophils, temperature [as a continuous variable and defined as fever/no fever at baseline > 38.0°C, hypothermia < 36.0°C]) will be summarized by treatment group. The percentage of subjects meeting the systemic inflammatory response syndrome (SIRS) criteria at baseline will also be provided (yes vs no). SIRS is defined as having 2 or more of the following criteria: temperature < 36°C or > 38°C, heart rate > 90 bpm, respiratory rate > 20 bpm, or WBC count < 4000 cells/mm^3 or > 12,000 cells/mm^3 or > 10% bands. Descriptive statistics of baseline lesion area and a summary of the local signs and symptoms will also be provided by treatment group separately by type of ABSSSI infection (actual as recorded on the eCRF. Differences between treatment groups will be analyzed using Fisher's exact test for dichotomous variables and the Wilcoxon Rank Sum test for ordinal and continuous variables.

For those subjects with a concurrent secondary ABSSSI, a summary or listing (depending on the number of subjects with a concurrent secondary ABSSSI) of the lesion type and organisms isolated will be provided by treatment group.

9.2.1 Baseline Microbiology

The microbiological assessment of the primary ABSSSI site specimen by the local laboratory will be summarized by treatment group for the mITT population. A frequency distribution of the specimen collection method, the number and percentage of subjects with no growth and growth will be presented.

The pathogenic organisms identified from the baseline blood culture or culture of the primary ABSSSI site will be presented. The number and percentage of subjects with Gram-positive organisms (aerobes and anaerobes) and with Gram-negative organisms (aerobes and anaerobes) will be presented by genus and species for the micro-mITT and ME populations. The same pathogen identified from both the blood and the culture of the ABSSSI will be counted only once in the summary. In addition, the number and percentage of subjects with mono-microbial Gram-positive and poly-microbial infections (Gram-positive only and mixed infections (Gram-positive and Gram-negative) will be provided overall and by type of infection (micro-mITT population only)

The percentage of subjects with a positive blood culture by pathogenic organism will be provided for the micro-mITT and ME populations. The number and percentage of subjects with a Gram-positive organism (aerobes and anaerobes) and with a Gram-negative organism (aerobes and anaerobes) will be presented by genus and species.

A listing will be provided that includes all baseline and post-baseline isolates obtained from the blood and ABSSSI site specimen and will indicate the type of specimen and pathogenic organism.

Several tables providing minimum inhibitory concentration (MIC) data will be provided for the micro-mITT and ME populations:

- The MIC distribution to omadacycline and linezolid, across treatment groups
- The MIC distribution to the test article received, by treatment group
- MIC summary statistics (ie, range, $MIC_{50,}$ and MIC_{90}) to the test article received. The MIC range will be provided for all baseline pathogens. The MIC_{50} and MIC_{90} will be provided only for those pathogens isolated at least 10 times in a treatment group.

The distribution of disk diffusion zone diameters (mm) will be provided for the test article received, by treatment group.

In all microbiology analyses, the following apply:

- If there are multiple specimens (of the same sample type) from the same time-point where the same pathogen is isolated, only the pathogen with the highest MIC to the test article

received will be used. If the pathogens have the same MIC to test article received, the one with the lowest accession number will be used. The Gram's stain associated with the selected pathogen will be utilized for analysis.

- If the same pathogen is identified from the blood and ABSSSI sample, for tables providing MIC or disk diffusion data, the pathogen with the highest MIC to the test article received will be used.
- MRSA and MSSA are considered distinct pathogens.
- Vancomycin susceptibility is provided for all *Enterococcus* spp. defined as pathogens. Vancomycin resistant and vancomycin susceptible isolates of each species are considered distinct pathogens (ie, vancomycin resistant *E. faecalis* and vancomycin susceptible *E. faecalis* are distinct)
- When per-subject counts of *Staphylococcus aureus* are presented, subjects with both MRSA and MSSA are counted only once.
- When per-subject counts of *Enterococcus* spp. pathogens are presented, subjects with both vancomycin susceptible and vancomycin resistant isolates of the same species are counted only once.

9.2.2 Primary Site Procedures and Care

Any procedures on the primary ABSSSI site will be recorded on the eCRF. All ABSSSI site procedures (eg, bedside I&D, operative I&D, aspiration, debridement, re-exam of the lesion in operating room, skin graft, incision without grafting, wound cleaning/lavage, amputation, interventional radiology, other) will be presented on a by subject listing. The percentage of subjects receiving each type of surgical procedure prior to the first dose of test article, from the first dose of test article through to the assessment of Early Clinical Response (Safety and mITT population), from the first dose of test article through to the EOT Visit (Safety, mITT and CE-EOT populations), and through to the PTE Visit (Safety, mITT and CE-PTE populations) will be presented by treatment group. The reasons for the surgical procedures from first dose of test article through the PTE Visit will also be provided for the mITT population.

9.3 Treatment Compliance and Exposure

Exposure summary by treatment group will be presented for the Safety, mITT, and CE-PTE populations. The distribution of subjects by the total number of days on therapy (1 to 3, 4 to 6, 7 to 10, 11 to 12, 13 to 14 and > 14 days) will be presented as will descriptive statistics for the total number of days on therapy.

Treatment compliance is defined as the number of active tablets actually received divided by the number of active tablets expected (× 100) over the time period defined by the first and last dose date. The last dose date is the last day the subject is expected to receive test article based on the length of therapy determined by the Investigator or the actual last date the subject took test article, if s/he prematurely discontinued test article due to treatment failure or an adverse event. Dose 2 can be missed per protocol if it cannot be taken a minimum of 8 hours after Dose 1 and a minimum of 8 hours before the expected time of Dose 3. Descriptive statistics for treatment

compliance and the number and percentage of subjects at least 80% compliant will be presented by treatment group for the mITT and Safety populations.

A summary of compliance with the pre- and post-dose fasting requirements will also be provided. The percent fasting compliance will be determined based on the total doses taken where fasting is required. The percentage of subjects who were < 50%, 50% to < 80%, and 80% to 100% compliance with the pre-dose and post-dose fasting requirements will be summarized for the mITT and Safety populations.

10 EFFICACY PARAMETERS

For all efficacy analyses, subjects will be analyzed in the group to which they were randomized. By definition, subjects who receive the wrong test article are not included in the CE-EOT, CE-PTE, ME-EOT and ME-PTE populations. Subjects who are randomized to the wrong infection type or prior antibiotic stratum will be analyzed in the stratum to which they were randomized, unless otherwise stated. A summary of the efficacy analyses is provided in Appendix 2.

10.1 Primary Analysis

The primary efficacy analyses will be based on the mITT population. The non-inferiority test will be a 1-sided hypothesis test performed at the 2.5% level of significance. This non-inferiority test will be based on the lower limit of the 2-sided 95% confidence interval (CI). The primary efficacy outcome is the percentage of subjects with an Early Clinical Success at 48 to 72 hours after the first dose of test article.

The number and percentage of subjects in each treatment group defined as an Early Clinical Success, Clinical Failure and Indeterminate (subjects with missing data or who are lost to follow-up) will be tabulated, as will the overall category combining Clinical Failure and Indeterminate. The null and alternative hypotheses are as follows:

$$H_0 : p_1 - p_2 \leq -\Delta \text{ and } H_1 : p_1 - p_2 > -\Delta,$$

where p_1 is the primary efficacy outcome rate in the omadacycline treatment group, p_2 is the primary efficacy outcome rate in the linezolid treatment group, and Δ is the non-inferiority margin of 10%.

To test the null hypothesis, a 2-sided 95% CI for the observed difference in primary outcome rates (omadacycline treatment group minus linezolid treatment group) will be calculated for the mITT population. If the lower limit of the 95% CI for the difference in the mITT population exceeds –10%, then the null hypothesis will be rejected and the non-inferiority of omadacycline to linezolid will be declared.

The 2-sided 95% CI for non-inferiority testing based on the difference of Early Clinical Success rates at 48 to 72 hours after the first dose of test article, will be computed using the method proposed without stratification by Miettinen and Nurminen[3]. For notation purposes, assume 1 represents the omadacycline group (Group 1) and 2 represents the linezolid group (Group 2).

Based on Miettinen and Nurminen, the 2-sided 95% CI is given by the roots for $RD = p_1 - p_2$ of the following equation:

$$\chi_\alpha^2 = \frac{(\hat{p}_1 - \hat{p}_2 - RD)^2}{V}$$

where χ^2_α is the cut point of size α from the chi-square distribution (χ^2_α=3.84 for 2-sided 95% CI); RD is the difference between the 2 true rates ($RD = p_1 - p_2$); $\hat{p}_1$ = the observed average proportion in Group 1; $\hat{p}_2$ = the observed average proportion in Group 2; and

$$V = \left[\frac{\tilde{p}_1(1-\tilde{p}_1)}{n_1} + \frac{\tilde{p}_2(1-\tilde{p}_2)}{n_2} \right] \frac{n_1 + n_2}{n_1 + n_2 - 1}$$

where n_1= number of subjects in Group 1; n_2= number of subjects in Group 2; $\tilde{p}_1 = \tilde{p}_2 + RD$; and $\tilde{p}_2$ is the maximum likelihood estimate for p_2 as a function of RD and under the constraint $p_1 = p_2 + RD$.

As stated above, the 2-sided 95% CI for the difference in rates is given by the roots for $RD = p_1 - p_2$ from the equation above, but this equation does not allow for explicit solution for RD. Therefore, a numerical algorithm will be used to obtain the 2 roots (CI) for RD. This CI approach corresponds to the non-inferiority test (a p-value approach) proposed by Farrington and Manning[2].

The reasons for Clinical Failure and reasons for Indeterminate response will be summarized by treatment group.

10.2 Sensitivity and Additional Analyses of the Primary Efficacy Outcome

Sensitivity analyses of the primary outcome include:

- Determination of the 95% CI adjusted for infection type and receipt of prior antibiotics. If there are < 20 subjects within a stratum and treatment group, or there is a 0 count within a stratum for a treatment group and outcome, wound and abscess will be combined. If the combining of the infection types is not sufficient to complete the adjusted analysis, the prior antibiotic strata will be combined into one group. The 95% CI interval will be computed using the stratified methodology of Miettinen and Nurminen. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI as follows, where n_{1i} = number of subjects in Group 1 in the ith stratum; n_{2i}= number of subjects in Group 2 in the ith stratum:

  $$W_i = \frac{n_{1i} n_{2i}}{n_{1i} + n_{2i}}$$

- The second sensitivity analysis of the primary outcome will consider all subjects who are lost to follow-up prior to a lesion size assessment from 46 to 72 hours or have missing data as an Early Clinical Success (these subjects are considered Indeterminates and analyzed as Clinical Failures in the primary analysis).
- A multiple imputation analysis using a Markov chain Monte Carlo full data imputation will be used to define missing data. Fifty data sets will be created using this technique in which type of infection (cellulitis/erysipelas, major cutaneous abscess and wound infection), prior receipt of antibiotics (yes and no), infection result of IV drug use, (yes and no) and baseline

lesion area (≤ 300 cm^2, > 300 to 600 cm^2, > 600 to 1000 cm^2, and > 1000 cm^2) are included as predictive variables.

10.3 Secondary Analysis

The number and percentage of subjects in each treatment group with a Clinical Success, Clinical Failure, and Indeterminate for the overall assessment of Clinical Response at the PTE Visit (based on the investigator's assessment) will be reported for the mITT and CE-PTE populations (by definition CE-PTE subjects cannot have a response of Indeterminate). Two-sided 95% CIs will be constructed for the observed differences in the Clinical Success rate using the method of Miettinen and Nurminen without stratification. The 95% CIs are for descriptive purposes only and no conclusion of NI will be made. The reasons for Clinical Failure will be summarized by treatment group.

The number and percentage of subjects in each treatment group in each response category for Early Clinical Response will be presented for the micro-mITT population. The number and percentage of subjects who are classified as a Clinical Success and Clinical Failure based on the overall assessment of Clinical Response at the PTE Visit (based on the investigator's assessment) in the ME-PTE population will be calculated. Two-sided 95% CI without stratification will be constructed for the observed difference in the Clinical Success rates using the method of Miettinen and Nurminen.

Early Clinical Response and the overall assessment of Clinical Response at the PTE Visit by baseline pathogen will be determined as the proportion of subjects with a Clinical Success, for each pathogen isolated at baseline for the blood culture or the culture of the ABSSSI site. The number and percentage of subjects in each treatment group with a Clinical Success (based on Early Clinical Response and investigator's assessment of response) will be tabulated per pathogen for the micro-mITT and ME-PTE (for investigator's assessment only) populations. Early Clinical Response and the overall assessment of Clinical Response at the PTE Visit in the micro-mITT and ME populations will also be provided by mono-microbial and poly-microbial infections (Gram-positive only and mixed infections [Gram-positive and Gram-negative]).

10.4 Additional Analyses

Additional efficacy analyses will be conducted to support the efficacy findings of the primary and secondary outcomes. CIs will be determined for descriptive purposes, but no conclusions of NI will be made.

Clinical Outcomes

The number and percentage of subjects classified as an Early Clinical Success, Clinical Failure and Indeterminate at 48 to 72 hours after the first dose of test article in the ITT population will be calculated. A 2-sided 95% CI without stratification will be constructed for the observed difference in the Clinical Success rate using the method of Miettinen and Nurminen.

The number and percentage of subjects classified as a Clinical Success, Clinical Failure and Indeterminate by the investigator's assessment at EOT in the mITT and CE-EOT populations (by

definition subjects with an Indeterminate response are excluded from the CE-EOT population) will be calculated for each treatment group. A 2-sided 95% CI without stratification will be constructed for the observed difference in the clinical success rate using the method of Miettinen and Nurminen.

A summary (number and percentage of subjects) of the shift from baseline to each visit (Day 2, Day 3, Day 7, Day 10, EOT and PTE Visits) in the clinical signs and symptoms (presence of drainage, tenderness, edema, erythema, induration) of the ABSSSI will be presented by treatment group for the mITT and CE-PTE populations. The number and percentage of subjects with resolution of all clinical signs and symptoms that were present at baseline will be presented for each visit throughout the study. The assessment of the systemic signs will also be summarized at each time point these were measured. This includes descriptive statistics of the WBC count, temperature and immature neutrophils as continuous variables, percentage of subjects with a WBC count $\geq$ 10,000 cells/mm^3 or < 4000 cells/mm^3, fever (defined as temperature > 38°C), > 15% neutrophils, presence of lymphadenopathy proximal to primary lesion site and presence of lymphangitis proximal to the primary lesion site.

Descriptive statistics of the primary infection site measurements (surface area [length x width]) will also be provided at each visit the infection site was measured for the mITT populations. The measurement at the visit, the absolute change from baseline, and the percent change from baseline will be provided at each visit. The percent change from baseline will be categorized as, < 0% (any increase), and decreases of 0 to < 5%, 5 to < 10%, 10 to < 15%, 15 to < 20%, 20 to < 30%, 30 to < 40%, 40 to < 50% and 50% to 100%.

All-cause mortality (ACM) at 30 days after randomization will be summarized in the ITT population. Subjects who are lost to follow-up will be excluded from this analysis.

Descriptive statistics of temperature will be provided for each visit temperature was measured for the mITT and CE-PTE population. The measurement at the visit and the absolute change from baseline will be provided at each visit, as will the percentage of subjects who have a temperature $\leq$ 37.8°C.

A concordance analysis of the primary efficacy outcome (Early Clinical Response at 48 to 72 hours) with the overall assessment of Clinical Response at the PTE Visit (based on the investigator's assessment) and the investigator's assessment of Clinical Response at the EOT Visit will be conducted in the mITT population. A concordance analysis of per-subject microbiological response and the investigator's assessment of Clinical Response at the EOT Visit will be conducted in the micro-mITT population.

For the micro-mITT and ME populations, the number and percentage of subjects with an Early Clinical Success (only micro-mITT population), with an assessment of Clinical Success (based on the investigator's assessment) at the EOT Visit (micro-mITT and ME-EOT populations) and an overall assessment of Clinical Success at the PTE Visit (based on investigator's assessment, micro-mITT and ME-PTE populations), will be tabulated by baseline MIC to omadacycline and linezolid by pathogen (for those pathogens occurring at least 5 times in one of the treatment groups) and treatment group.

Microbiological Outcomes

The per-subject microbiological response at the EOT and PTE Visits in the micro-mITT, ME-EOT (EOT Visit only) and ME-PTE (PTE-Visit only) populations will be determined to support the clinical findings. The number and percentage of subjects classified with a favorable (eradication and presumed eradication) and unfavorable (persistence, presumed persistence, and indeterminate) microbiological response (by definition, indeterminates are excluded from the ME population) will be tabulated for both treatment groups. A 2-sided 95% CI without stratification will be constructed for the observed difference in the per-subject favorable microbiological response rate between the omadacycline and linezolid groups using the method of Miettinen and Nurminen.

Per-subject microbiological response at the PTE Visit in the micro-mITT and ME-PTE populations will also be provided by mono-microbial and poly-microbial infections (Gram-positive only and mixed infections [Gram-positive and Gram-negative]).

Microbiologic response by baseline pathogen will be determined as the proportion of subjects with a favorable microbiological response (eradication or presumed eradication) at the EOT and PTE Visits for each pathogen isolated at baseline from the blood culture or culture of the ABSSSI site. The number and percentage of subjects in each treatment group with a microbiologically favorable outcome will be tabulated for the micro-mITT, ME-EOT (EOT Visit) and ME-PTE (PTE Visit) populations. Favorable microbiologic response by baseline pathogen will also be summarized separately for pathogens obtained from the blood culture (ie, for bacteremic subjects) for the micro-mITT population.

Microbiological categories for pathogens identified after baseline assessment are superinfection and new infection. The number and percentage of subjects with a superinfection or new infection will be presented by treatment group. A listing will be provided that presents the subjects with a superinfection and new infection including the type of specimen and pathogen.

Decreasing susceptibility of a pathogen is defined as a 4-fold increase from baseline to any subsequent study time point in the MIC of the test article received. The number and percentage of subjects in the micro-mITT population with a pathogen showing decreasing susceptibility will be tabulated for each treatment group. In addition, a table will list all subjects in each treatment group with a pathogen showing decreasing susceptibility, including the type of specimen, pathogen, and MIC values. Additional exploratory microbiological analyses may be conducted.

Subject Reported Outcomes

At the Screening, Day 3, EOT and PTE visits the subject will complete a numerical rating scale for pain[4] (average pain over the last 24 hours) at the primary ABSSSI lesion site. The numerical rating scale anchors will range from 0 to 10, where 0 represents “No pain” and 10 represents “Pain as bad as you can imagine.” Descriptive statistics of the numerical rating scale for pain at each time point and the change from baseline for each time point will be provided by treatment group for the mITT population.

At the Screening and PTE visits the subject will complete a SF-36v2® Health Survey (Medical Outcomes Trust, Optum™). The SF-36v2® Health Survey asks 36 questions to measure functional health and well-being from the subject's point of view. The SF-36v2® Health Survey consists of 8 scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health) which are weighted sums of the questions in their section. Each scale is transformed into a 0 to 100 scale with the lower the score the more disability. There are 2 composite scores: physical and mental. Descriptive statistics for the composite scores and each subscale will be provided for baseline, the PTE visit and the change from baseline by treatment group for the mITT population.

Subject reported outcomes will be analyzed independently from other data collected in the study.

10.5 Interim Analysis

No interim analysis of efficacy or safety is planned.

10.6 Subgroup Analyses

The primary analysis (ECR) results will be assessed separately across infection type and prior antibiotic stratum by treatment group for both the as randomized strata and the actual strata as indicated on the eCRF. For each infection type stratum, and each prior antibiotic stratum, a 2-sided 95% CI for the observed difference in the early clinical success rates will be calculated for the mITT population. If a clinically meaningful treatment group-by-infection type or treatment group-by-prior antibiotic result in the opposite direction of the overall result is noted, an inferential test may be performed as a descriptive statistic.

Additional subgroup analyses of the primary efficacy outcome will also be conducted for descriptive purposes. These include, but are not limited to clinical site, bacteremic subjects, subjects with SIRS, size of lesion (≤ 300 cm^2, > 300 to 600 cm^2, > 600 to 1000 cm^2, and > 1000 cm^2), receipt of NSAIDs from first dose of test article through the assessment of early clinical response, and receipt of an operative incision and drainage. Two-sided 95% CIs for the observed difference in the early clinical success rates will be calculated for the mITT analysis set for each subgroup as descriptive analyses. Exploratory analyses in other subgroups may also be conducted.

Results of the overall assessment of Clinical Response at the PTE Visit (based on the investigator's assessment at the EOT and PTE Visits) will also be assessed across infection type and prior antibiotic by treatment group for both the as randomized strata and the actual strata as indicated on the eCRF. Separately for each infection type stratum and for each prior antibiotic stratum, 2-sided 95% CIs for the observed difference in clinical response in the mITT and CE-PTE populations will be calculated. If a clinically meaningful treatment group-by-infection type or treatment group-by-prior antibiotic result in the opposite direction of the overall result is noted, an inferential test may be performed as a descriptive statistic.

11 SAFETY AND TOLERABILITY

All safety analyses will be conducted in the Safety population. Subjects who receive the wrong test article for their entire course of treatment will be analyzed in the group based on the drug received. If a subject receives both omadacycline and linezolid, the subject will be analyzed in the omadacycline arm regardless of the amount of omadacycline received or the randomized treatment assignment. Safety parameters include adverse events (AEs), vital signs, electrocardiogram (ECG) parameters and clinical laboratory parameters.

11.1 Adverse Events

Verbatim descriptions of AEs will be coded using Version 17.1 or higher of MedDRA. Summary tables will be provided for all treatment-emergent adverse events (TEAEs) but all AEs will be provided in a listing. A treatment-emergent AE is defined as any AE that newly appeared, increased in frequency, or worsened in severity on or after the initiation of active test article. An AE is considered treatment emergent if the AE start date and time is on or after the start date and time of the first dose of active test article. If time of the AE is missing and it occurred on the same date as the first dose of active test article, the AE will be defined as treatment emergent. If the start date of the AE is partial or missing and it cannot be determined if the AE occurred prior to or after the first dose of test article, the AE should be defined as treatment emergent.

An overall summary of AEs will include the number of subjects who experienced at least one AE of the following categories: any AE, any TEAE, any drug-related TEAE, any severe TEAE, any serious TEAE, any drug-related SAE, any serious TEAE leading to death, any TEAE leading to premature discontinuation of test article, any TEAE leading to premature discontinuation from the study, any TEAE leading to dose interruption of test article, and any serious TEAE leading to premature discontinuation of test article.

The number and percentage of subjects reporting a TEAE in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity (mild, moderate, and severe); and by system organ class, preferred term, and relationship (unrelated or related to test article). The incidence of TEAEs will be summarized by preferred term and treatment group, sorted by decreasing frequency in the omadacycline group, for all TEAES, related TEAEs, serious TEAEs and TEAEs leading to test article discontinuation. The incidence of serious TEAEs and TEAEs leading to premature discontinuation of test article, will be summarized by system organ class and preferred term. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to test article.

TEAEs occurring (ie, with a start date and time) during the time period subjects are on treatment will be summarized by system organ class and preferred term.

In addition, all AEs (including non-TEAEs), serious TEAEs, and TEAEs leading to discontinuation of test article will be provided in listings by treatment group, study site, subject, verbatim term, MedDRA system organ class and preferred term, start and end date, seriousness

flag, severity, relationship to test article, relationship to study protocol, action taken with test article, non-test article action taken and outcome.

For subjects with a TEAE of nausea (based on the MedDRA preferred term), the total number of nausea events, descriptive statistics of the study day of onset of all nausea events, and descriptive statistics for the duration (in days) of all nausea events, will be presented by treatment group.

11.2 Vital Signs

Blood pressure (systolic and diastolic), respiratory rate and pulse/heart rate will be summarized using descriptive statistics at the following time points: baseline, Day 1, Day 2, Day 3, Day 7, Day 10, the EOT visit and PTE visit, but not the final Follow-up Visit. Pulse rate and blood pressure will be summarized for the following additional time points: a) 30 minutes before, 1 hour after and 3 hours after the completion of the first dose on Day 1, and b) 30 minutes before and 1 hour after and 3 hours after the completion of the odd numbered doses on Days 2 and 3. In the event the subject takes the dose before arriving at the office visit, the site should collect the 1 and 3 hour post dose measurements, if possible. If not then a single measurement at any time during the visit should be obtained.

Descriptive statistics of the change from baseline to each post-baseline time point will also be provided. Baseline is defined as the value closest to but prior to the initiation of test article administration. If no value is available prior to the initiation of test article administration, a value within 2 hours after initiation of test article administration can be used as baseline. The change from baseline to the minimum and maximum post-baseline values (including any unscheduled post-baseline assessments) will also be summarized by treatment group.

Figures (line graphs) of value and change from baseline for systolic and diastolic blood pressure, and heart rate by time point will also be provided by treatment group.

Post-baseline vital signs will be defined as clinically notable (CN) if they meet 1) the criterion value or 2) meet both the criterion value and the change from baseline criterion listed in Table 8. The incidence of CN vital signs will be summarized by time point and treatment group, and will be listed and flagged in by-subject listings. The overall post-baseline incidence of CN values for each vital sign parameter, which includes values from unscheduled post-baseline visits, will also be summarized. A listing will also be provided of subjects with a CN vital sign and will list all values for a vital sign noted as CN.

Table 8. Criteria for Treatment Emergent Clinically Notable Vital Signs

Vital Sign Parameter	Flag	Criterion Value	Change from Baseline
Systolic Blood Pressure (mmHg)	High (CH)	≥ 180	Increase of ≥ 20 mmHg
	Low (CL)	≤ 90	Decrease of ≥ 20 mmHg
Diastolic Blood Pressure (mmHg)	High (CH)	≥ 105	Increase of ≥ 15 mmHg
	Low (CL)	≤ 50	Decrease of ≥ 15 mmHg
Heart Rate (bpm)	High (CH)	≥ 120	Increase of ≥ 15 bpm
	Low (CL)	≤ 50	Decrease of ≥ 15 bpm

11.3 Electrocardiogram

A central vendor with readers blinded to treatment assignment will perform the reading of the ECGs. The central ECG results will be used for the statistical analyses.

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) at baseline and at the EOT Visit, and the change from baseline will be presented by treatment group. The QTc interval will be presented by both the Bazett ($QTcB = QT/(RR)^{1/2}$) and the Fridericia ($QTcF = QT/(RR)^{1/3}$) corrections. The change from baseline to the minimum and maximum post-baseline values (including EOT and any unscheduled post-baseline assessments) will also be summarized by treatment group. Baseline is defined as the value closest to but prior to the initiation of test article administration. If no value is available prior to the initiation of test article administration, a value within 2 hours after initiation of test article administration can be used as baseline.

The number and percentage of subjects with any post-baseline (including EOT and any unscheduled post-baseline assessments) increase in QTcF and any post-baseline increase of > 30 msec or > 60 msec in QTcF will be summarized by treatment group. The number and percentage of subjects with a baseline QTcF ≤ 450 msec and with a post-baseline QTcF of > 450 msec and with a baseline QTcF ≤ 500 and with a post-baseline QTcF of > 500 msec will also be summarized by treatment group. The number and percentage of subjects with a post-baseline increase in QTcF of > 30 msec resulting in a post-baseline QTcF of > 450 msec or > 500 msec will also be summarized by treatment group. A listing will also be provided of subjects with a QTcF that meets one of the criteria listed above and will list all QTcF values for the subject.

The distribution of QTcF values (≤ 450 msec, > 450 to ≤ 480 msec, > 480 to ≤ 500 msec, and > 500 msec) at each time point and the distribution of change from baseline in QTcF values at EOT (0 or less [no increase], 1 to 29 msec, 30 to 60 msec, and > 60 msec) will be summarized by treatment group.

11.4 Laboratory Values

Summaries of laboratory data will include hematology, chemistry and coagulation (INR only) parameters. Laboratory parameters will be presented in alphabetic order with the following exceptions: differentials of white blood cell (WBC) counts will be presented following the WBC results, and chemistry parameters will first be grouped by organ class (renal, liver, electrolytes, and other) and presented alphabetically within each of these classes, as shown in Table 9.

Table 9. Laboratory Parameters and Organ Class

Organ Class	Laboratory Parameter
Renal	Creatinine
Renal	Urea
Liver	Alkaline phosphatase (ALP)
Liver	ALT
Liver	AST
Liver	Total Bilirubin
Liver	GGT
Electrolytes	Bicarbonate
Electrolytes	Calcium
Electrolytes	Chloride
Electrolytes	Magnesium
Electrolytes	Potassium
Electrolytes	Sodium
Other	Albumin
Other	Amylase
Other	Blood glucose
Other	Cholesterol
Other	CK
Other	CK isoenzyme
Other	LDH
Other	Lipase
Other	Phosphate
Other	Total protein
Other	Uric acid

Baseline is defined as the central lab value closest to and prior to the first dose of test article. If no central lab value is available prior to the first dose of test article the local lab value that is closest to and prior to the first dose of test article will be used as baseline. For by visit analyses, central lab values will be used unless no central lab value was obtained in the visit window. In this case, local lab values will be used for the by visit analyses. All lab values (central and local) are used for determination of the overall worst post-baseline value.

Several analyses of the laboratory data will be presented. Descriptive statistics (based on SI units) for chemistry and hematology values and the change from baseline will be summarized by treatment group at each time point (Day 3 [+ 1 day], Day 7 [+1 day], Day 10 [+1 day], EOT visit and PTE visit), and for the overall worst value post-baseline (which includes unscheduled visits). Appendix 4 provides the directionality of the worst values for each laboratory parameter.

Clinically notable laboratory values will be determined based on the modified Division of Microbiology and Infectious Diseases (DMID) criteria in Appendix 5. Shift tables will be presented to show the number of subjects with a laboratory value with a grade of 0, 1, 2, 3 or 4 at baseline versus the value at each visit and the worst post-baseline value. Number and percentage of subjects with at least a 2 grade increase from baseline (based on DMID criteria) will be summarized by treatment arm. Percentages for each laboratory test will be based on the number of subjects with a baseline and post-baseline evaluation of the specific laboratory test. A listing

will be provided which gives all laboratory results for a given laboratory test for subjects who have at least a 2 grade increase from baseline.

The number and percentage (based on the number of subjects with a normal level at baseline) of subjects in each treatment group with an elevated transaminase level (> 3 × ULN, > 5 × ULN, and >10 × ULN), an elevated bilirubin level (>1.5 × ULN and >2 × ULN) will be presented by study visit. A table will list all subjects with any post-baseline ALT or AST > 3x ULN or total bilirubin >1.5 x ULN. The table will provide the AST, ALT, total bilirubin and alkaline phosphatase value for each subject at each time point laboratory values were entered. A listing of subjects who meet the laboratory criteria for Hy's law will also be provided. The laboratory criteria for Hy's law is defined as 1) ALT or AST > 3 × ULN, ALP ≤ 2.0 × ULN, and total bilirubin > 1.5 x ULN and 2) ALT or AST > 3 × ULN, ALP ≤ 2.0 × ULN, and total bilirubin > 2 × ULN.

Detailed subject listings of all laboratory data (local and central laboratory data) collected during the study will be provided, including calculated creatinine clearance (using the Cockcroft-Gault equation). Laboratory values outside normal limits will be identified in the subject data listings with flags for low (L) and high (H) as will laboratory values that meet the clinically notable thresholds (CN).

11.5 Physical Examinations

Subject listings of all physical examination results by body system will be provided. Any changes from baseline will be recorded as adverse events.

12 RESOURCE UTILIZATION ANALYSES

Descriptive statistics of the following resource utilization parameters will be provided by treatment group:

- Number of hospitalizations for the ABSSSI from the first dose of study drug through the FU Visit.
- For those subjects who had at least one hospitalization, the number of days in the hospital from date of admission for the ABSSSI until discharge.

13 OTHER RELEVANT DATA ANALYSES/SUMMARIES

13.1 Protocol Deviations

A listing of all protocol deviations will be provided. Deviations will also be reviewed by the sponsor and categorized into general categories such as: randomization, at least one inclusion criterion not met, at least one exclusion criteria met, study procedures/visits not done, study visit outside window, use of prohibited medications or treatments, consent-IRB compliance issues, etc. The sponsor will also categorize the protocol deviations as major and minor. Review of protocol deviations will be conducted and finalized prior to unblinding the database. The number of subjects with at least one protocol deviation, the number of subjects with a minor protocol deviation, the number of subjects with a major protocol deviation, and the number of subjects with at least one major protocol deviation in each category will be presented by treatment group for the ITT population. A major deviation is defined as one that potentially affects the efficacy and/or safety analyses.

13.2 Prior and Concomitant Medications

All medications taken within 7 days prior to the date of informed consent through the Final Follow-up Visit will be recorded on the e-CRF. Prior medications will be summarized by WHODRUG (Version 01-Dec-2014) Anatomical Therapeutic Chemical Classification (ATC) level 3 (third level indicates the therapeutic/pharmacologic subgroup) and generic medication name. Medications are considered prior if taken prior to the first dose of test article or if their start date is unknown. Subjects will be counted only once for an ATC class and generic medication name. Concomitant medications taken during and after the study treatment period will be similarly summarized. Medications are considered concomitant if taken on or after the first dose of test article, or if their stop date is unknown or marked as continuing.

The proportion of subjects who receive the following prior and concomitant medications will be summarized by treatment group:

- Systemic and topical antibacterial medications taken within 7 days prior to first dose of test article and the reasons for receipt (mITT and CE-PTE populations)
- Systemic single dose, short-acting, non-oxazolidinone antibacterial taken within 72 hours prior to randomization
- Systemic and topical antibacterial medications (excluding test article) taken between first dose of test article and the EOT Visit (CE-EOT population) and the reasons for receipt (mITT and CE-EOT populations)
- Systemic and topical antibacterial medications (excluding test article) taken between first dose of test article and the PTE Visit (CE-PTE population) and the reasons for receipt (mITT and CE-PTE populations)
- Non-antibacterial medications taken 7 days prior to informed consent through the first dose of test article (mITT and Safety populations)

- Non-antibacterial medications taken from the first dose of test article through the Final Follow-up Visit (mITT and Safety populations)

14 REFERENCES

1 Prokocimer P, De Anda C, Fang E, Mehra P, Das A. 2013. Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections: The ESTABLISH-1 Randomized Trial. JAMA. 309:559-69.

2 Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med. 1990 Dec;9(12):1447-54.

3 Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine. 1985;4(2):213-26.

4 McCaffery, M, Beebe, A. 1993. Pain: Clinical Manual for Nursing Practice. Baltimore: V.V. Mosby Company.

15 APPENDICES

Appendix 1 Schedule of Events

Study Phase	Screening[a]	Double-Blind Treatment Phase						Follow-up Phase	
Study Day[b]		Day 1	Day 2	Day 3 (ECR 48-72 hr after first dose)	Day 7	Day 10[c]	EOT[d]	PTE[e]	Final Follow-up[f] Day 30-37
Signed Informed Consent[g]	X								
Demographics	X								
Medical/surgical history and current medical conditions	X								
Prior and concomitant medications[h]	X	X----------							----------X
Clinical assessment of the site of infection[i]	X		X	X	X	X	X	X	
Assessment of lesion size[j]	X		X	X	X	X	X	X	
Diagnosis of ABSSSI and photograph of the lesion site[k]	X								
Numerical Rating Scale for pain at the primary lesion site	X			X			X	X	
SF-36v2® Health Survey	X							X	
Physical examination[l]	X						X	X	
Vital signs									
Respiratory rate	X	X	X	X	X	X	X	X	
Body temperature	X	X	X	X	X	X	X	X	
Blood pressure	X	X[m]	X[n]	X[n]	X	X	X	X	
Pulse/heart rate	X	X[m]	X[n]	X[n]	X	X	X	X	
12-lead ECG[o]	X						X		
Urine dipstick test[p]	X								
Urine pregnancy test[q]	X								
Serum pregnancy test[r]	X						X	X	
Hematology[s]	X[t]			X	X	X	X	X	
Serum chemistry[s]	X[t]			X	X	X	X	X	
Blood culture[u]	X			As Clinically Indicated			X[v]	X[v]	
Culture of infection site & Gram stain	X			As Clinically Indicated			X[v]	X[v]	
Adverse Events[w]	X	X----------							----------X

Study Phase	Screening[a]	Double-Blind Treatment Phase						Follow-up Phase	
Study Day[b]		Day 1	Day 2	Day 3 (ECR 48-72 hr after first dose)	Day 7	Day 10[c]	EOT[d]	PTE[e]	Final Follow-up[f] Day 30-37
Review of Inclusion and Exclusion Criteria/Randomization (if Eligible)	X								
Test Article Administration and Accountability[x]		X[y]	X[z]	X[aa]	X	X			
Plasma samples (in heparin) for PK analyses[bb]			X	X					
Assessment of need to continue therapy[cc]					X	X			
Investigator's Assessment of Clinical Response							X	X	

ABSSSI = Acute Bacterial Skin and Skin Structure infection; AE = adverse event; β-hCG = beta – human Chorionic Gonadotropin; ECG = electrocardiogram; ECR = Early Clinical Response; eCRF = electronic case report form; EOT = end of treatment; ICF = informed consent form; PK = pharmacokinetics; PTE = post therapy evaluation; SAE = serious adverse event.

[a] Following the signing of an ICF, all Screening evaluations, with the exception of the blood culture sample collection, should be completed within the 24 hours prior to randomization. The blood culture sample collection should be completed within 24 hours prior to the first dose of test article.

[b] Day 1 is the first day of test article administration. Subsequent study days are consecutive calendar days.

[c] A Day 10 visit should be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the EOT visit.

[d] To be conducted on the calendar day of, or within 2 days following the last dose of test article. Should also be conducted for any subject who withdraws prematurely or terminates participation in the study before completion.

[e] To be conducted 7 to 14 days after the subject's last day of study therapy.

[f] To be conducted 30 to 37 days after the first dose of test article. The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be Clinical Successes and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the PTE visit. Otherwise, the visit must be conducted in person.

[g] Written and signed ICF must be obtained before any assessment is performed.

[h] Treatments that have been administered within the 7 days prior to the date of signing the ICF or during the Screening phase will be recorded in the eCRF. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the first dose of test article must be recorded in the eCRF.

[i] Semi-quantitative description of infection features. Must be assessed within 48 to 72 hours after the first dose.

[j] Measurement of the subject's lesion by ruler length × width. The Screening measurement must be collected within 4 hours prior to randomization. A lesion measurement must be completed within 48 to 72 hours after the first dose.

[k] Diagnosis of the type of ABSSSI (wound infection, cellulitis/erysipelas or major abscess) and anatomical location. A digital photograph of the infection site will be taken at Screening only.

[l] A full physical examination will be completed at Screening; thereafter only changes from Screening measurements should be recorded as AEs in the eCRFs.

[m] Blood pressure and pulse rate should be measured within 30 min before, and approximately (± 15 minutes) 1 hour after and 3 hours after the completion of the first dose on Day 1.

[n] Blood pressure and pulse rate should be measured within 30 min before, and approximately (± 15 minutes) 1 hour after and 3 hours after the completion of the odd numbered doses on Days 2 and 3. In the event that the subject takes the dose before arriving for the office visit, the site should collect the 1 and 3 hour post dose measurements if possible, if not then a single measurement should be made at any time during the visit and the date and time recorded.

[o] A 12-lead ECG should be performed at screening, at the EOT visit, and as otherwise clinically indicated.

[p] A urine dipstick test will be performed locally at Screening.

[q] All women will have a local urine pregnancy test at Screening.

[r] All women will have blood collected for a serum β-hCG pregnancy test at the Central Laboratory at the Screening, EOT and PTE visits.

[s] Blood will be collected for hematology (includes coagulation) and serum chemistry testing at the Central Laboratory at Screening and at the Day 3, Day 7, Day 10, EOT and PTE visits.

[t] At the Screening visit, blood will be collected for local laboratory hematology and serum chemistry evaluations required for assessing subject eligibility.

[u] If bacteria are isolated from blood cultures, repeat blood cultures should be collected. If subsequent blood cultures are also positive, repeat the blood cultures as necessary until negative blood cultures are obtained.

[v] At the EOT and/or PTE visit, blood cultures and infection site specimen cultures and Gram stains should be obtained only for subjects who are clinical failures and require alternative antibacterial treatment for the infection under study.

[w] A subject's AEs and SAEs will be recorded and reported from signing of the ICF to the Final Follow-up assessment.

[x] A 6 hour fast is required before and a 2 hour fast is required following all odd numbered doses. The total duration of test article therapy for all subjects will be 7 to 14 days. Test article may be dispensed and reconciled by blinded personnel. Subjects will be asked to return all unused test article and packaging at each visit. At the EOT visit subjects will return the test article packaging and site staff will perform accountability.

[y] Subjects should receive their first dose of test article at the site within 4 hours after randomization.

[z] Subjects should be instructed not to take the odd numbered dose on Day 2 until they return to the site for the Day 2 visit.

[aa] Subjects should be instructed not to take the odd numbered dose on Day 3 until they return to the site for the Day 3 visit.

[bb] At selected sites, subjects who have agreed to participate in PK evaluation and have signed a separate PK evaluation consent form will have up to 4 blood samples collected between Days 2 and 3. The PK sample collection schedule for the individual subject will be provided by the Sponsor.

[cc] At the investigator's discretion, all therapy may be discontinued after the 7th day of treatment, when the infection is considered clinically cured (based on normalization of the clinical signs and symptoms of infection and the investigator's clinical assessment that continued systemic antibacterial therapy is no longer needed).

Appendix 2 Summary of Efficacy Analyses

	48-72 Hours Post First Dose	End of Treatment Visit (EOT)	Post Therapy Evaluation Visit (PTE)
ITT	ECR		
mITT	ECR (primary efficacy)	IA	IA
Micro-mITT	ECR	Micro (by subject)	IA (by pathogen)
	ECR (by pathogen)	Micro (by pathogen)	IA (by pathogen and MIC)
	ECR (by pathogen and MIC)		Micro (by subject)
			Micro (by pathogen)
CE-EOT		IA	
CE-PTE			IA
ME-EOT		Micro (by subject)	
		Micro (by pathogen)	
ME-PTE			IA
			IA (by pathogen)
			IA (by pathogen and MIC)
			Micro (by subject)
			Micro (by pathogen)

ECR = Early Clinical Response; IA = Investigator Assessment of Response.

Appendix 3 Adverse Event and Prior/Concomitant Medication Date Imputations

Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of test article	Date of first dose of test article
		M and/or Y not same as date of first dose of test article	First day of month
	D and M	Y same as Y of first dose of test article	Date of first dose of test article
		Y prior to Y of first dose of test article but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of test article
Stop date for AEs	D	M and Y same as M and Y of last dose of test article	Date of last dose of test article
		M and/or Y not same as date of last dose of test article	Use last day of month
	D and M	Y same as Y of last dose of test article	Date of last dose of test article
		Y not same as Y of last dose of test article	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.
In all cases, if it cannot be determined if the adverse event occurred prior to or after the first dose of test article, the adverse event should be defined as treatment emergent.

Prior and Concomitant Medication Start Date Imputation

Parameter	Type of Medication	Imputation
Start date for con meds	Non-Antibacterial	If it cannot be determined whether or not the start date of a medication (non-antibacterial) is prior to the first dose of test article, it will be assumed that the medication was received prior to the first dose of test article
	Antibacterial	Missing start dates for antibacterials will be queried for a value. If it cannot be determined whether or not the start date of an antibacterial is prior to the first dose of test article, it will be assumed that the medication was received prior to the first dose of test article unless the indication notes that the medication was received after the first dose of test article.
Stop date for con meds	Non-Antibacterial	If it cannot be determined whether or not the stop date of a medication (non-antibacterial) is after the first dose of test article, it will be assumed that the medication was received after the first dose of test article
	Antibacterial	Missing stop dates for antibacterials will be queried for a value. If it cannot be determined whether or not the stop date of an antibacterial is after the first dose of test article, it will be assumed that the medication was received after the first dose of test article unless the indication notes that the medication was received prior to the first dose of test article. If it cannot be determined whether the antibacterial was received prior to the assessment of Early Clinical Reponse, the EOT and/or the PTE Visit, the antibacterial will be assumed to have been received through the PTE Visit.

Appendix 4 Directionality of Worst Laboratory Parameters

Laboratory Test	Parameter	Worst Value
Hematology	Hematocrit	Lowest value
	Hemoglobin	Lowest value
	Red blood cell count	Lowest value
	Mean cell hemoglobin	Lowest value
	Mean cell hemoglobin concentration	Lowest value
	Mean cell volume	Lowest value
	White blood cell count	Lowest value
	Platelets	Lowest value
	Neutrophils	Lowest value
	Lymphocytes	Lowest value
	Monocytes	Lowest value
	Eosinophils	Highest value
	Basophils	Lowest value
Chemistry	Albumin	Lowest value
	Alkaline phosphatase	Highest value
	Alanine aminotransferase ALT/SGPT)	Highest value
	Amylase	Highest value
	Aspartate aminotransferase (AST/SGOT)	Highest value
	Urea	Highest value
	Bicarbonate	Lowest value
	Calcium	Both highest value and lowest value
	Cholesterol	Highest value
	Chloride	Both highest value and lowest value
	Creatinine	Highest value
	Creatine kinase (CK)	Highest value
	Gamma-glutamyl transpeptidase (GGT)	Highest value
	Blood glucose	Both highest value and lowest value
	Lactate dehydrogenase (LDH)	Highest value
	Lipase	Highest value
	Magnesium	Both highest value and lowest value
	Phosphate	Both highest value and lowest value
	Potassium	Both highest value and lowest value
	Sodium	Both highest value and lowest value
	Total bilirubin	Highest value
	Total protein	Lowest value
	Uric acid	Highest value
Coagulation	International normalized ratio (INR)	Highest value

Appendix 5 Modified Division of Microbiology and Infectious Diseases Adult Toxicity Table

The DMID Adult Toxicity Table (21-Nov-2007) was modified to exclude the clinical component of the toxicity grading because clinical signs and symptoms related to abnormal laboratory values are not collected in this study. In addition, Grade 0 was added to the table so that shifts from normal could be analyzed. The grades for several parameters including enzymes were modified to ensure that any possible numeric value can be categorized appropriately (eg, for creatinine, Grade 3 is defined as ">1.5-3.0×ULN" instead of "1.6-3.0×ULN").

For toxicity grades based on a multiple of the ULN, the normal range from the central laboratory will be applied.

For toxicity grades based on fixed values, the grades will be assigned regardless of the normal actual range values from the central laboratory. For example, a hemoglobin value of 10.0 gm/dL will be assigned a grade of 1 toxicity, even if the lower limit of normal from the laboratory was 9.8 gm/dL.

HEMATOLOGY

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (gm/dL)	> 10.5	9.5-10.5	8.0-9.4	6.5-7.9	< 6.5
Absolute Neutrophil Count (count/mm^3)	> 1500	1000-1500	750-999	500-749	< 500
Platelets (count/mm^3)	≥ 100,000	75,000-99,999	50,000-74,999	20,000-49,999	< 20,000
WBCs (count/mm^3)	1000-10,999	11,000-12,999	13,000-14,999	15,000-30,000	> 30,000 or < 1,000

COAGULATION

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Prothrombin time (PT) (sec)	≤1 x ULN	1.01-1.25 x ULN	1.26-1.5 x ULN	1.51 x 3.0 x ULN	> 3 x ULN
Activated partial thromboplastin time (aPTT) (sec)	Increased	≤ ULN	1.01 - 1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN
International normalized ratio (INR)	Increased	≤ ULN	> 1 - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN

CHEMISTRY

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia (mEq/L)	> 135	130-135	123-129	116-122	< 116
Hypernatremia (mEq/L)	< 146	146-150	151-157	158-165	> 165
Hypokalemia (mEq/L)	> 3.4	3.0-3.4	2.5-2.9	2.0-2.4	< 2.0
Hyperkalemia (mEq/L)	< 5.6	5.6-6.0	6.1-6.5	6.6-7.0	> 7.0
Hypoglycemia (mg/dL)	≥ 65	55-64	40-54	30-39	< 30
Hyperglycemia (mg/dL) (nonfasting and regardless of prior history of diabetes)*	< 116	116-160	161-250	251-500	> 500
Hypocalcemia (mg/dL) (corrected for albumin)*	> 8.4	8.4-7.8	7.7-7.0	6.9-6.1	< 6.1
Hypercalcemia (mg/dL) (correct for albumin)*	≤ 10.5	10.6-11.5	11.6-12.5	12.6-13.5	> 13.5
Hypomagnesemia (mEq/L)	> 1.4	1.4- 1.2	1.1-0.9	0.8-0.6	< 0.6
Hypophosphatemia (mg/dL)	≥ 2.5	2.0-2.4	1.5-1.9	1.0-1.4	< 1.0
Hyperbilirubinemia (total bilirubin)	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.5×ULN	> 2.5-5×ULN	> 5×ULN
Urea	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	>10×ULN
Hyperuricemia (uric acid) (mg/dL)	< 7.5	7.5–10.0	10.1–12.0	12.1–15.0	> 15.0
Creatinine	< 1.1×ULN	1.1-1.5×ULN	> 1.5-3.0×ULN	> 3.0-6×ULN	> 6×ULN

*The DMID toxicity table reports hyperglycemia detected in nonfasting specimens obtained from subjects with no prior diabetes.

ENZYMES

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
ALT (SGPT)	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
GGT	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Alkaline Phosphatase	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Amylase	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.0×ULN	> 2.0-5.0×ULN	> 5.0×ULN
Lipase	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.0×ULN	> 2.0-5.0×ULN	> 5.0×ULN

* Calcium corrected for albumin = [0.8 x (normal albumin - subject's albumin)] + serum Ca level
Where normal albumin = 4 g/dl, albumin is in g/dL and calcium is in mg/dL