STATISTICAL ANALYSIS PLAN

A Phase 2, Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Contezolid Acefosamil Compared to Linezolid Administered Intravenously and Orally to Adults with Acute Bacterial Skin and Skin Structure Infection

Study: MRX4-201

CONFIDENTIAL

May 28, 2019

STATISTICAL ANALYSIS PLAN APPROVAL
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31 May 2019

Denis Boisvert, MS — Date

Study Statistician

InClin, Inc.

DocuSigned by:

Signer Name: Edward Fang
Signing Reason: I approve this document
Signing Time: 5/31/2019 2:32:07 PM PDT
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31 May 2019

Edward Fang, MD — Date

SVP, Clinical Development

MicuRX Pharmaceuticals, Inc.

DocuSigned by:

Signer Name: Amy Bassett
Signing Reason: I approve this document
Signing Time: 6/3/2019 8:47:04 AM PDT
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03 June 2019

Amy Bassett, MPH — Date

Study Director

MicuRX Pharmaceuticals, Inc.

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1 Abbreviations and Definitions

1.1 Abbreviations:

Abbreviation	Definition
ABSSSI	Acute bacterial skin and skin structure infection
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical class
BMI	Body Mass Index
CACO	Composite assessment of clinical outcome
CE	Clinically evaluable
CI	Confidence interval
CN	Clinically Notable
CSR	Clinical Study Report
CRO	Contract Research Organization
CTCAE	Common Terminology for Adverse Events
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic case report form
GGT	Gamma-glutamyl transferase
GM	Geometric Mean
H	High
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web response system
L	Low

Abbreviation	**Definition**
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
MAOI	Monoamine oxidase inhibitor
MAX	Maximum
ME	Microbiologically evaluable
MIC	Minimum Inhibitory Concentration
MIC50	Minimum Inhibitory Concentration to inhibit the growth of 50%
MIC90	Minimum Inhibitory Concentration to inhibit the growth of 90%
MIN	Minimum
MITT	Modified intent-to-treat
micro-ITT	Microbiological intent-to-treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
NRL	Normalized Range Low
NRH	Normalized Range High
PK	Pharmacokinetic
PO	Oral
PT	Preferred term
QD	Once daily
QTcF	Corrected QT interval using the Fridericia correction formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

Abbreviation	Definition
WBC	White blood cell count
WHO	World Health Organization

1.2 Definitions of Terms:

Term	Definition
CACO	Combined outcome of early response at EA and Investigator's assessment of clinical outcome at PTE
Contezolid	The active metabolite of contezolid acefosamil moiety (formerly known as MRX-1)
Contezolid acefosamil	The investigational medicinal product in this study (formerly known as MRX-4); a prodrug that undergoes a 2-step conversion process to contezolid (active moiety) by means of MRX-1352 (an intermediate metabolite)
Dose	Any amount of drug (IV or PO) taken at the time of dosing.
EA	Early assessment (48 to 72 hours after the start of the first dose of IV study drug)
EOT	End of therapy (last day of study drug)
LFU	Late follow-up (21-28 days after EOT)
MRX-1320	A primary metabolite of contezolid; MRX-1320 is also known as "M2" in other documents
MRX-1352	Intermediate metabolite in the 2-step process by which prodrug (contezolid acefosamil) is converted into contezolid (active moiety)
PTE	Post therapy evaluation (7 to 14 days after EOT)
Subject	An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control

2 Introduction

This document presents the Statistical Analysis Plan (SAP) for the protocol MRX4-201, "A Phase 2, Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Contezolid Acefosamil Compared to Linezolid Administered Intravenously and Orally to Adults with Acute Bacterial Skin and Skin Structure Infection". The statistical plan described is an a priori plan and no analyses have been conducted prior to the preparation of this plan. 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 MRX4-201. Changes made to the SAP after it has been signed but prior to study unblinding will be documented in an amendment. Any important changes made to the analyses will be described in the clinical study report (CSR). This SAP is based on the original protocol version dated August 16, 2018, protocol amendment 1 dated September 27, 2018, and protocol amendment 2 dated October 19, 2018.

3 Study Design

This is a Phase 2, multicenter, randomized, double-blind safety and efficacy study of contezolid acefosamil 1500 IV x 1 dose, followed by 1000 mg IV every 12 hours (q12h) (± 2 hours), for at least 3 total IV doses, followed by 1300 mg PO q12h (± 2 hours) compared with linezolid 600 mg IV q12h (± 2 hours), for at least 3 total IV doses, followed by 600 mg PO q12h (± 2 hours) in adult subjects with ABSSSI. Subjects will receive study drug for a total of 10 to 14 days.

Up to 200 subjects will be enrolled to achieve approximately 150 clinically evaluable subjects in the CE-PTE population with ABSSSI from approximately 5 to 10 sites in the US. Randomization will have a 2:1 (contezolid acefosamil: linezolid) allocation ratio; therefore, up to 133 subjects will be randomized to receive contezolid acefosamil and up to 67 subjects will be randomized to receive linezolid. Efforts will be made to enroll a mixture of ABSSSI types (cellulitis/erysipelas, wound infection, and major cutaneous abscess); however, subjects with major cutaneous abscess should not comprise > 30% of randomized subjects. Subjects will be randomized to treatment provided they meet all inclusion and no exclusion criteria. Randomization will be stratified by ABSSSI type to better ensure proper balance between the treatment groups.

Subjects may receive adjunctive antimicrobial therapy with parenteral aztreonam (1 to 2 g IV/ intramuscular [IM] q8h, not to exceed 6 g/day) if the Investigator suspects or has confirmed the presence of aerobic Gram-negative pathogens, which, in addition to Gram-positive aerobic bacteria, are also associated with the pathogenic process. Subjects with only Gram-negative pathogens are not eligible for continued treatment under this protocol and will be discontinued from study drug as soon as Gram stain and culture confirms that the subject's infection has no Gram-positive pathogen contributing to the subject's disease.

Subjects who received prior systemic antibacterial therapy with Gram-positive activity within 96 hours prior to randomization will be excluded from the study unless clear clinical evidence of prior treatment failure within the prior 96 hours is available. However, one exception to this criterion is the receipt of a single dose of a short-acting, non-oxazolidinone antibiotic (as provided in the study exclusion criteria and list of allowable antibiotics). Subjects who received a single dose of a short-acting non-oxazolidinone Gram-positive active antibiotic within 96 hours prior to randomization will not comprise > 25% of randomized subjects.

Randomized subjects will receive at least 3 doses of treatment with IV study drug followed by PO dosing, however subjects may receive the IV formulation for the entire treatment duration. Study treatment will be as follows:

- Subjects randomized to contezolid acefosamil treatment will receive IV infusions of contezolid acefosamil q12h (± 2 hours) for a minimum of 3 infusions followed by 2 PO contezolid acefosamil capsules q12h (± 2 hours) for a total of 10 to 14 days of treatment. The IV dose of contezolid acefosamil will be 1500 mg infused over 60 minutes (± 5 minutes) for 1 dose followed by 1000 mg infused over 60 minutes (± 5 minutes); the PO dose of contezolid acefosamil will be 1300 mg (2 capsules each with 650 mg of contezolid acefosamil).
- Subjects randomized to linezolid treatment will receive IV infusions of linezolid q12h (± 2 hours) for a minimum of 3 infusions followed by 2 PO linezolid capsules q12h (± 2 hours) for a total of 10 to 14 days of treatment. The IV dose of linezolid will be 600 mg infused over 60 minutes (± 5 minutes); the PO dose of linezolid will be 600 mg (2 capsules each with 300 mg of linezolid).

Subjects may receive the IV formulation for the entire treatment duration. The primary ABSSSI lesion will be recorded in the eCRF at the screening/baseline visit. If the primary ABSSSI lesion has not increased in area from the screening/baseline assessment and the Investigator determines that the subject has sufficient PO intake of food and drink to safely support the administration of PO doses of antibiotics, the subject may be switched to the PO formulation. Subjects will undergo follow-up visits as described in Table 1 in an outpatient setting to assess the safety, tolerability, and efficacy of the investigational products.

Day 1 is the first day of study drug administration; subsequent study days are consecutive calendar days. For purposes of analysis, Early Assessment (EA) will be performed 48 to

72 hours after the start of the first dose of IV study drug, End of Therapy (EOT) will occur on the last calendar day of study drug (+ 1 day), Post Therapy Evaluation (PTE) will occur 7 to 14 days after EOT, and Late Follow-up (LFU) will occur 21 to 28 days after EOT.

Subjects will receive study drug for 10 to 14 days. Subjects will then be followed for up to 28 days after the last calendar day of study drug. Therefore, the total duration of each subject's participation in the study will be up to 42 days, excluding the screening/baseline visit that occurs within 24 hours prior to study drug administration on Day 1. The study design is shown schematically in Table 1 and a detailed "Schedule of Study Procedures" is provided in Appendix A

Table 1: Schedule of Study Procedures

Screening/ Baseline	**Study Treatment Period (Day 1 to EOT)**				**PTE**	**LFU**
Within 24 hours prior to first dose	Day 1	EA (48-72 hours)	Day 7 (± 1 day)	EOT (+ 1 day)	7-14 days after EOT	21-28 days after EOT
Confirm eligibility; Baseline clinical, laboratory, and safety assess-ments	Randomize to treatment First dose of study drug Safety assessments PK samples (Days 1-2)[a]	Clinical, laboratory, and safety assessments	Clinical, laboratory, and safety assessments	Last dose of study drug Clinical, laboratory, and safety assessments PK samples [a]	Clinical, laboratory, and safety assessments	Investigator's assessment of clinical relapse/failure and AE assessment

EA = early assessment; EOT = end of therapy; IV = intravenous; LFU = late follow-up; PK = pharmacokinetic; PTE = post therapy evaluation
a PK sampling will be sparse. Samples will be collected after the first IV dose and prior to and after the third IV dose (i.e. on Day 1 and Day 2) and at completion of therapy (IV or PO), as described in the Pharmacokinetic Assessments section.

Subjects who discontinue study drug or withdraw from the study itself will undergo all EOT assessments on the day of study drug discontinuation or study withdrawal (+ 1 day). Subjects who discontinue study drug will remain in the study and complete all assessments specified for the PTE and LFU visits. For subjects who withdraw from the study, efforts will be made to perform follow-up safety assessments per study schedule. None of the subjects will be replaced once they have been randomized. The duration of treatment within the specified window will be determined by the Investigator based on the subject's clinical status (e.g., therapy can be discontinued if the subject has improved, no more antibiotic treatment is medically necessary, and the risk of relapse is minimal).

Gram stain and culture specimens of the ABSSSI site will be collected from all subjects for microbiologic evaluation at screening/baseline. ABSSSI site specimens (purulent discharge, skin biopsy, or aspiration at the leading edge of the cellulitis area) in addition to blood cultures from 2 separate venipuncture sites will be obtained from all subjects prior to administration of antibacterial therapy whenever possible. ABSSSI specimen culture and Gram stains will be repeated at subsequent visits only if clinically indicated (e.g., subject is deemed a clinical failure or if purulence and discharge from the ABSSSI site continues after screening/baseline). Blood cultures must be repeated every 3 days (+/- 1 day) if the previous blood culture was positive or at any time after screening/baseline if clinically indicated.

4 Study Objectives

4.1 Primary Objectives

The primary objectives are as follows:

- Evaluate early clinical response of contezolid acefosamil compared to linezolid at early assessment (EA; 48 to 72 hours after the start of the first dose of IV study drug) in the intent-to-treat (ITT) population
- Evaluate safety and tolerability of both contezolid acefosamil IV and PO formulations compared with linezolid

4.2 Secondary Objectives

The secondary objectives are as follows:

- Evaluate early clinical response at:
  - EA in the modified intent-to-treat (MITT) population
  - EA (overall and by baseline pathogen) in the microbiological intent-to-treat (micro-ITT) population
- Evaluate percent reduction in lesion size from baseline in ABSSSI lesions at Day 7 in the ITT and MITT populations
- Evaluate the Investigator's assessment of clinical response in the ITT, MITT, and clinically evaluable (CE) populations at each timepoint:
  - End of therapy (EOT; last day of study drug) in the ITT, MITT, and CE-EOT populations

  - Post therapy evaluation (PTE; 7 to 14 days after EOT) in the ITT, MITT, and CE-PTE populations
  - Late follow-up (LFU; 21-28 days after EOT) in the ITT, MITT, and CE-PTE populations
- Evaluate per-subject microbiological response at:
  - PTE in the micro-ITT population
  - PTE in ME population
- Evaluate per-pathogen microbiological response at:
  - PTE in the micro-ITT population
  - PTE in the ME population
- Evaluate Investigator's assessment of clinical response in the micro-ITT and ME populations at:
  - PTE (overall and by baseline pathogen)
  - LFU (overall and by baseline pathogen)
- Characterize the PK of 3 contezolid acefosamil metabolites (MRX-1352, contezolid, and MRX-1320) using sparse PK sampling in adult subjects with ABSSSI
- Evaluate composite assessment of clinical outcome (CACO) in the ITT, micro-ITT, and CE-PTE populations

5 Data Management

Data management procedures, including database design, development of the data dictionary, and coding of medical history, adverse events and medications, will be performed at a Contract Research Organization (CRO). Data will be entered into an electronic case report form (e-CRF) at the study sites. A series of logic and consistency checks will be conducted to ensure accuracy and completeness of the clinical database. Safety laboratory results, microbiology data, electrocardiogram data, and pharmacokinetic data will be electronically transmitted from external vendors. After database lock, randomization data will be provided electronically from the IWRS vendor. Refer to the Data Management Plan for further Data Management details.

6 Pathogen Determination

Pathogens will be identified 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.

Screening/baseline samples are collected within 24 hours of the first dose of study drug on either Day 1 or Day -1. If more than one baseline ABSSSI site sample was obtained using a an acceptable ABSSSI specimen (purulent discharge, skin biopsy, or aspiration at the leading edge of the cellulitis area) or more than one baseline blood sample was obtained, isolates from all samples will be reviewed for pathogen determination. 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, then a Day 2 or 3 ABSSSI site sample can be used as baseline if the sample is considered acceptable.

The organisms identified in Table 2 will always be considered a pathogen when isolated from an acceptable ABSSSI specimen. Additional pathogens will be identified during pathogen review prior to unblinding of the study.

Table 2: ABSSSI Pathogens

• *Enterococcus faecalis*	• *Enterococcus faecium*
• *Escherichia coli*	• *Group C beta-hemolytic streptococci*
• *Klebsiella pneumoniae*	• *Methicillin-resistant Staphylococcus aureus (MRSA)*
• *Methicillin-susceptible Staphylococcus aureus (MSSA)*	• *Proteus mirabilis*
• *Pseudomonas aeruginosa*	• *Staphylococcus haemolyticus*
• *Staphylococcus lugdunensis*	• *Streptococcus agalactiae*
• *Streptococcus anginosus*	• *Streptococcus constellatus*
• *Streptococcus dysglactiae*	• *Streptococcus intermedius*
• *Streptococcus pyogenes (Group A streptococci)*	• *Streptococcus viridans group*

The following organisms will never be considered a pathogen when isolated from an ABSSSI specimen:

Table 3: Not ABSSSI Pathogens

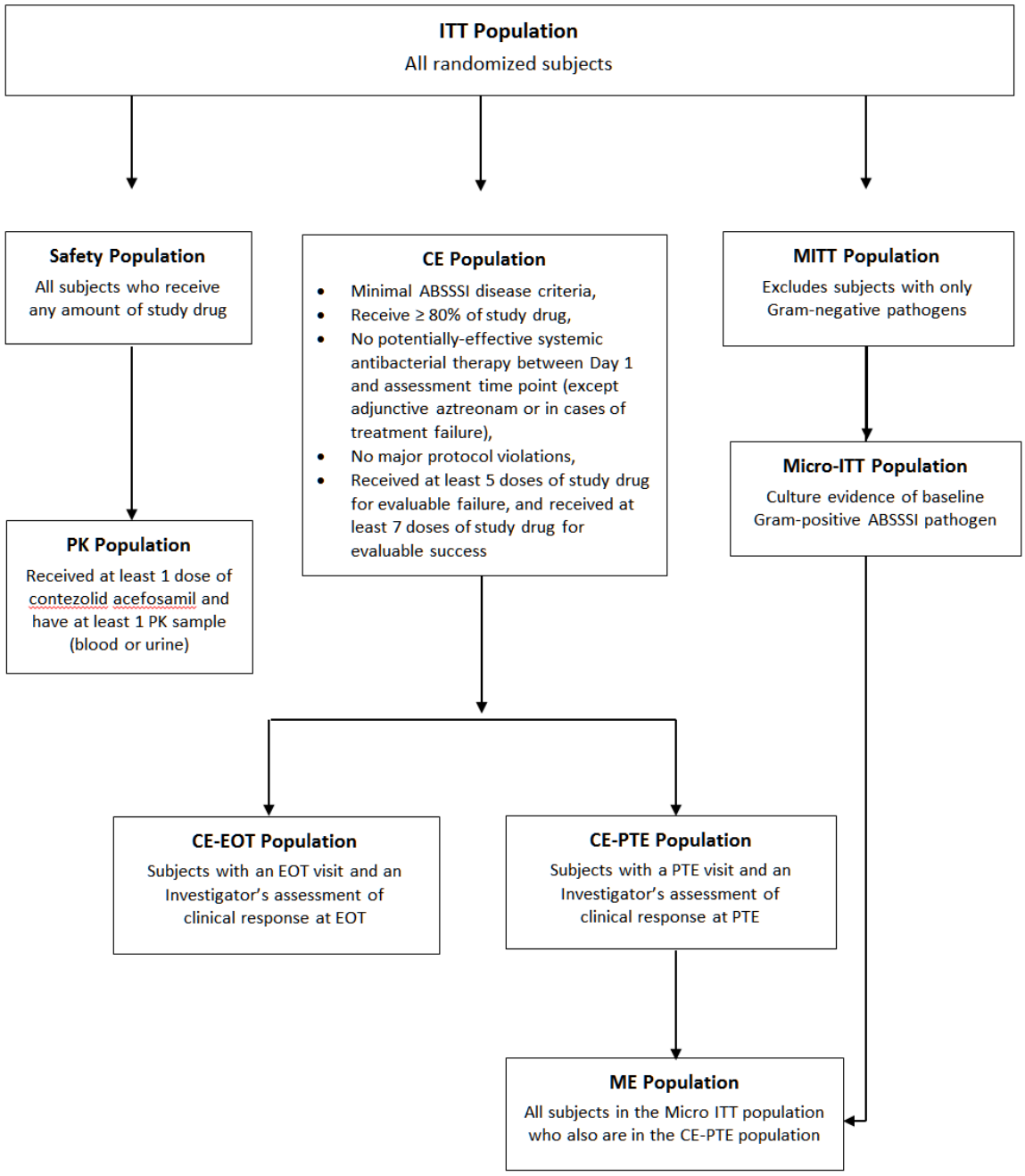
• *Bacillus* spp.	• *Candida* spp. or other fungi
• *Corynebacterium* spp.	• *Micrococcus* spp.
• *Staphylococcus epidermidis*	• *Staphylococcus hominis*
• *Staphylococcus saprophyticus*	• *Staphylococcus warneri*

All other organisms not listed above will be assessed on a case-by-case basis via manual review by the Sponsor (e.g., Gram-negative organisms, anaerobes). If needed, subject clinical (e.g., type of infection, type of specimen, subject underlying conditions, etc.) and microbiological information (e.g., Gram stain, etc.) will be used to assist in determining if the isolate is a pathogen. In addition, all polymicrobial infections (i.e., ABSSSI caused by more than 1 pathogen) and all cases of bacteremia will be reviewed manually.

7 Definition of Analysis Populations

The relationship between the analysis sets is shown in Figure 1 below.

Figure 1: Overview of Analysis Populations



ABSSSI = acute bacterial skin and skin structure infection; CE = clinically evaluable; EOT = end of therapy; ITT = intent-to-treat; ME = microbiologically evaluable; micro-ITT = microbiological intent-to-treat; MITT= modified intent-to-treat; PK = pharmacokinetic; PTE = post therapy evaluation

7.1 Intent-to-Treat (ITT) Population

The ITT population will consist of all randomized subjects regardless of whether or not the subject received study drug. A subject is considered randomized when the Investigator or Investigator's designee receives the IWRS-generated randomization number.

7.2 Modified Intent-to-Treat (MITT) Population

All randomized subjects in the ITT population, excluding subjects with only a Gram-negative pathogen(s) at baseline.

7.3 Safety Population

The Safety population will consist of all randomized subjects who receive any amount of study drug. All safety analyses will be conducted in this population and will be presented in the summary tables by the treatment the subject actually received. In the event that a subject received both contezolid acefosamil and linezolid then that subject will be included in the contezolid acefosamil arm.

7.4 Microbiological Intent-to-Treat (Micro-ITT) Population

The Micro-ITT population will consist of all subjects in the ITT population who have culture evidence of a baseline Gram-positive bacterial pathogen known to cause ABSSSI. Analyses in this population will be presented in summary tables by the treatment arm to which the subject was randomized.

7.5 Clinically Evaluable Population at End-of-Therapy (CE-EOT) and the Post-Therapy Evaluation (CE-PTE)

The CE-EOT and CE-PTE populations will consist of all subjects in the ITT population who:

- meet the minimal clinical disease criteria for ABSSSI described in the study Inclusion Criteria (Protocol Section 4.1),
- receive at least 80% of expected doses based on length of therapy,
- did not receive any potentially-effective systemic or topical antibacterial therapies other than protocol specified study drug(s) for an indication other than ABSSSI between Day 1 and timepoint for assessment (except for adjunctive aztreonam or in cases of treatment failure), where the timepoint for assessment is EOT for the CE-EOT population and PTE for the CE-PTE population.
- Did not have major protocol violations including but not limited to:

- Prior administration of systemic antibacterial therapy within 96 hours before randomization Exceptions: Subjects may be eligible if they meet the following conditions, either:

  ▪ Received a single dose of a non-oxazolidinone, short-acting, systemic antibiotic within 96 hours prior to randomization (Appendix 1). Note that such subjects will not comprise > 25% of randomized subjects

  or both of the following:

  ▪ Objective clinical evidence of treatment failure (persistent pain, erythema, induration, purulent drainage) following at least 48 hours of prior, non-study, systemic antibacterial therapy

  and

  ▪ Microbiological evidence of failure (i.e., a Gram stain obtained from an appropriate ABSSSI specimen collected after the initiation of this prior therapy revealing WBC and Gram-positive cocci, or isolation of a Gram-positive pathogen from an appropriate ABSSSI specimen that is resistant to the prior systemic antibacterial therapy)

- Received the wrong study drug or unblinded before the timepoint of assessment for reasons other than safety

In addition, to be included in the CE-EOT population, the following conditions must be met:

- Have an Investigator's assessment of clinical response at EOT (i.e., response can't be indeterminate)
- Had an EOT visit within 1 calendar day of last dose of study drug (+1 day) [i.e., within 48 hours of the last dose of study drug]

To be included in the CE-PTE population, the following conditions must be met:

- Have an Investigator's assessment of clinical response at PTE (i.e., response can't be missing or indeterminate unless the subject is deemed a clinical failure at the EOT visit)
- Had a PTE visit within 7-14 days after the EOT visit unless the patient was considered a failure at either EOT or PTE based on the Investigator's assessment of

clinical response. If the EOT visit is out of the study window, then the PTE visit must still be within 7-14 days of the EOT visit. If the EOT visit is missed, then the PTE visit must be within 7-14 days of the last dose of study drug.

Additional minimal dose requirements for clinical failure or success at EOT or PTE:

- Subjects who are defined as clinical failures at EOT or PTE with fewer than 5 doses of study drug are not included in the CE-EOT or CE-PTE populations, respectively.
- Subjects who are defined as clinical successes at EOT or PTE with fewer than 7 doses of study drug are not included in the CE-EOT or CE-PTE populations, respectively.

7.6 Microbiologically Evaluable Population (ME)

The ME Population includes all subjects in the CE-PTE Population with culture evidence of a baseline Gram-positive bacterial pathogen known to cause ABSSSI (i.e., meets both CE-PTE and Micro-ITT Population definitions).

7.7 Pharmacokinetic Population (PK)

All subjects who receive at least 1 dose of contezolid acefosamil and had at least 1 blood sample collected for analysis of MRX-1352, contezolid, or MRX-1320.

7.8 Evaluability Determination

The Medical Monitor 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. The Medical Monitor will be blinded to treatment assignment and will review the data concurrent with the conduct of the study.

Inclusion into the ITT and Safety Populations will be determined programmatically from the eCRF data. Inclusion into the CE-EOT and CE- PTE Populations will be determined programmatically from the eCRF data and manual review conducted by the Medical Monitor. The Medical Monitor may review subject data to confirm that population criteria are satisfied.

Inclusion into the MITT and ME Populations will be determined programmatically by incorporating the outcome of the review of the isolates by the Medical Monitor. The Medical Monitor will determine whether each isolate (baseline and post-baseline) is considered a pathogen based on a review of information from samples including infection type, type of specimen, Gram stain results, and local and central laboratory genus and species

identification. In the event that a local culture is completed, but a central lab culture not available, then the local lab result will be used.

8 Definition of Outcome Measures

8.1 Clinical Outcome Definitions

8.1.1 Programmatic Clinical Response at Early Assessment (Day 3 or Day 4) (EA)

Clinical response at EA will be determined programmatically based on data recorded on the e-CRF. Note that the protocol EA visit window is 48-72 hours after the first dose of study drug, but the window is extended to the lower bound of 46 hours for analysis purposes.

A subject will be classified programmatically as a 'responder at EA' if the percent reduction in the primary ABSSSI lesion area is greater than or equal to 20% compared to baseline, and the subject did not receive a systemic antibacterial agent with activity against Gram-positive organisms for the treatment of ABSSSI through 72 hours, and did not die of any cause within 72 hours of the first dose of study drug.

A subject will be classified programmatically as a 'non-responder at EA' if the percent reduction in the primary ABSSSI lesion size is less than 20% compared to baseline, or the subject received a systemic antibacterial agent with activity against gram-positive organisms for the treatment of ABSSSI through 72 hours, or died of any cause within 72 hours of the first dose of study drug.

A subject will be classified programmatically as 'indeterminate at EA' if study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up, or if the EA visit is out of the 46-72 hour window). If there is more than one ABSSSI measurement within the 46-72 hour window, the last measurement will be used to assess the clinical response at EA.

If the baseline lesion measurement is missing and there is one within 6 hours of the first dose of study drug, this measurement may be considered the baseline measurement.

8.1.2 Investigator Assessment of Clinical Response at End-of-Therapy (EOT)

Investigator-determined 'clinical success at EOT' is defined by all of the following:

- Resolution or near resolution of most baseline ABSSSI symptoms and signs,

- No new signs, symptoms, or complications attributable to the ABSSSI,
- No post-baseline surgical procedure through EOT, to treat the infection that was not already planned at baseline,
- No inter-current non-protocol specified systemic antibacterial therapy with activity against Gram-positive organisms for the treatment of ABSSSI, and
- Did not die of any cause up to EOT.

Investigator-determined 'clinical failure at EOT' is defined by any of the following:

- Lack of resolution or near resolution of most baseline ABSSSI symptoms and signs,
- New signs, symptoms, or complications attributable to the ABSSSI,
- No post-baseline surgical procedure through EOT, to treat the infection that was not already planned at baseline,
- Inter-current non-protocol specified antibacterial therapy administered for the treatment of the primary ABSSSI lesion or might have potential antibiotic activity directed toward the Gram-positive pathogens implicated in the ABSSSI, or
- Died of any cause up to EOT.

Investigator-determined 'Indeterminate at EOT' is defined as:

- Study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up).

8.1.3 Investigator-Assessment of Clinical Response at Post-therapy Evaluation (PTE)

Investigator-determined 'clinical success at PTE' is defined by all of the following:

- Resolution or near resolution of most baseline ABSSSI symptoms and signs,
- No new signs, symptoms or complications attributable to the ABSSSI,
- No post-baseline surgical procedure through PTE, to treat the infection that was not already planned at baseline,
- No inter-current non-protocol specified systemic antibacterial therapy with activity against Gram-positive organisms for the treatment of ABSSSI, and

- Did not die of any cause up to PTE.

Investigator-determined 'clinical failure at PTE' is defined by any of the following:

- Lack of resolution or near resolution of most baseline ABSSSI symptoms and signs,
- New signs, symptoms, or complications attributable to the ABSSSI,
- No post-baseline surgical procedure through PTE, to treat the infection that was not already planned at baseline,
- Inter-current non-protocol specified antibacterial therapy administered for the treatment of the primary ABSSSI lesion or might have potential antibiotic activity directed toward the Gram-positive pathogens implicated in the ABSSSI, or
- Died of any cause up to PTE.

Investigator-determined 'Indeterminate at PTE' is defined as:

- Study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up).

The following overall assessment of clinical response based on the Investigator's Assessment will be determined at the PTE Visit based on the following rules.

Table 4: Overall Assessment of Clinical Response

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

8.1.4 Investigator Assessment of Clinical Response at Late Follow-up (LFU)

Investigator-determined 'sustained clinical success' at LFU is defined as no new signs or symptoms of primary ABSSSI after PTE, while 'clinical relapse/failure' is defined as new or worsened signs or symptoms of primary ABSSSI after PTE. All cases of 'clinical relapse/failure' will be queried to ensure that an antibiotic was taken. If study data is unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up) then the result is 'indeterminate'. For analysis purposes, the worst assessment at EOT, PTE, or LFU will be summarized at LFU, where Failure is a worse outcome than an Indeterminate result. For example, if the responses are Success, Failure, and Indeterminate at EOT, PTE, and LFU, then the worst assessment of Failure will be summarized at LFU.

8.1.5 Composite Assessment of Clinical Outcome (CACO)

The CACO will be programmatically determined from the programmatic assessment of early clinical response at the EA visit and the Overall Assessment of Clinical Response at PTE based on the Investigator's assessment of clinical response at PTE as identified in Table 5.

Table 5: Composite Assessment of Clinical Outcome

Early Clinical Response at EA Visit	Overall Assessment of Clinical Response at PTE Visit	Composite Assessment of Clinical Outcome (CACO)
Responder	Success	Success
Responder	Failure	Failure
Responder	Indeterminate	Indeterminate
Nonresponder	Success	Failure
Nonresponder	Failure	Failure
Nonresponder	Indeterminate	Failure
Indeterminate	Success	Indeterminate
Indeterminate	Failure	Failure
Indeterminate	Indeterminate	Indeterminate

EA = early assessment; PTE = post therapy evaluation

8.2 Microbiologic Response

8.2.1 Per-Pathogen Microbiological Response at EOT and PTE Visits

Pathogen microbiological outcome categories are: eradication, presumed eradication, persistence, presumed persistence, and indeterminate and these as defined in the following table. Favorable microbiological outcomes include eradication or presumed eradication. Unfavorable microbiological outcomes include persistence or presumed persistence and are defined in Table 6.

Table 6: Pathogen Microbiological Response at EOT and PTE Visits

Eradication	An adequate source specimen (from ABSSSI site and/or blood) demonstrates absence of the original screening/baseline pathogen(s). If there is a positive blood sample at screening/baseline, the last blood sample on or prior to the referenced visit (*) must be a negative.
Presumed eradication	An adequate source specimen was not available to culture and the subject was assessed as a clinical success by the Investigator at the referenced visit (*). If there is a positive blood sample at screening/ baseline but there is no post-baseline blood sample available and the subject was assessed a clinical success by the Investigator at the referenced visit (*), then categorize as presumed eradication.
Persistence	An adequate source specimen demonstrates continued presence of the original baseline pathogen(s) (i.e., presence of original baseline pathogen cultured from the site of ABSSSI or blood) at the referenced visit (*).
Presumed persistence	An adequate source specimen was not available to culture from site of ABSSSI or blood and the subject was assessed as a clinical failure by the Investigator at the referenced visit (*).
Indeterminate	An adequate source specimen was not available to culture from site of ABSSSI or blood and the subject's clinical response was assessed as indeterminate at the referenced visit (*).

Note: Should EA or Day 7 pathogen results of 'no growth' be present for a subject, but no subsequent pathogens captured for the same subject, then the 'no growth' (i.e. eradication) results will be carried forward to EOT and PTE.

(*) the term referenced visit is EOT when defining the Pathogen Microbiological Response at EOT, and is PTE when defining the Pathogen Microbiological Response at PTE.

8.2.2 Per-Subject Microbiological Response at PTE and Overall Assessment at PTE

In order for a subject to have a favorable per-subject microbiological response, the outcome for each baseline pathogen must be favorable (eradicated or presumed eradicated). In order for a subject to have an unfavorable per-subject microbiological response, the outcome for any baseline pathogen must be unfavorable (persistence, presumed persistence).

The proportion of subjects with a favorable microbiological response is defined as:

$$P_{Micro\ Fav\ Resp} = \frac{(\#\ subjects\ wih\ eradication\ or\ presumed\ eradication)}{All\ subjects\ (including\ indeterminates)}$$

The overall assessment of microbiological response will be implemented using responses at the EOT and PTE visits as identified in Table 7

Table 7: Overall Assessment of Microbiological Response

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
Favorable is defined as eradication or presumed eradication.		

Unless otherwise specified, all summaries of microbiological response are based on the overall microbiologic response at PTE.

8.3 Emergent Infections

Microbiological definitions of superinfections or new infections are defined in Table 8.

Table 8: Superinfections and New Infections

Category	Definition
Superinfection	Isolation of a new pathogen(s) (other than the original screening/baseline pathogen[s]) from the primary ABSSSI site (culture) which is accompanied by signs and symptoms of infection requiring alternative systemic antimicrobial therapy during the period up to and including EOT, based on the Investigator's assessment of clinical response.
New infection	Isolation of a new pathogen(s) (other than the original screening/baseline pathogen[s]) from the primary ABSSSI site (culture) which is accompanied by signs and symptoms of infection requiring alternative systemic antimicrobial therapy after EOT, based on the Investigator's assessment of clinical response.

Abbreviations: ABSSSI= acute bacterial skin and skin structure infection; EOT = End of Therapy;

8.4 Safety Outcomes

Safety will be assessed through the determination and recording of the occurrence of adverse events (AEs) and AEs of special interest including, but not limited to hematology related AEs and neuropathies, as well as by adverse changes in vital signs, ECG parameters, and laboratory data. Hematology evaluations, serum chemistries, and urinalysis will be performed at screening/baseline, EA, Day 7 (± 1 day), EOT (+ 1 day), and PTE. Additional safety events that occur after PTE will be assessed at LFU. Adverse events will be evaluated by relationship to study drug and severity. Serious adverse events (SAEs) will be identified.

8.5 Pharmacokinetic Outcomes

Pharmacokinetic data will be collected at the time points specified in the protocol and details of the analysis of this data will be provided separately.

9 Statistical Methods and General Considerations

9.1 Sample Size

This study is not powered for inferential statistical analysis and the purpose is to allow for planning of future studies. No formal comparisons between treatment groups will be conducted. Up to 200 (133 contezolid acefosamil : 67 linezolid) adult subjects with ABSSSI will be enrolled in this study. If the responder rate is 0.8 at EA using early clinical response in the contezolid acefosamil group, then 133 evaluable subjects results in a 95% confidence interval (CI) of (0.72, 0.86) for the responder rate.

9.2 Randomization and Masking

Permuted block randomization using an interactive response system (IWRS) will be used to assign subjects (2:1) to contezolid acefosamil or linezolid. Randomization will be stratified by infection type. After informed consent has been obtained and study eligibility established, the study site's Pharmacist or Pharmacist's designee will obtain the subject number and the study drug assignment from a computer-generated randomization code via IWRS. A subject is considered randomized when the Pharmacist or Pharmacist's designee receives the randomization number or study drug assignment.

This is a double-blind study. Those blinded to study drug assignment include the Sponsor, Investigator, study statistician, clinical study personnel participating in subjects' care or clinical evaluations, and the subjects. Those unblinded to study drug assignment include the pharmacy personnel, the unblinded study monitor, and the bioanalytical laboratory. Blinded personnel must not make any effort to determine which study drug therapy is being administered. Blinded personnel will remain blinded to study drug assignment until all subjects have completed the study and the database is locked. Procedures to ensure that the blind is maintained are detailed in the Sponsor, CRO, and Vendor Blinding plan, the Blinded Clinical Monitoring Plan, and the Site-Specific Blinding Plans.

If study drug is determined not to be safe and tolerated, the study drug assignment for those subjects with a safety concern may be unblinded after discussion between the Investigator and Sponsor. The blind may also be broken in the case of a medical emergency requiring the Investigator to know the identity of the study drug to appropriately guide the subject's medical management. Prior to any unblinding, the Investigator is strongly advised to discuss options with the Medical Monitor or appropriate Sponsor study personnel. If the blind is

broken for any reason and the Investigator was unable to contact the Sponsor before unblinding, the Investigator must notify the Sponsor as soon as possible, without revealing the subject's study drug treatment assignment (unless important to the safety of subjects remaining in the study). All instances of unblinding will be thoroughly investigated and documented by the unblinded study monitor.

After the database is locked and the SAP is final, and all analysis populations have been determined, the study will be unblinded.

9.3 Interim Analysis

There is no formal interim analysis of efficacy or safety for this study and a Data Monitoring Committee (DMC) will not be utilized.

9.4 Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Baseline - A baseline value is the last non-missing value recorded prior to the first dose of study drug. For subjects who never get dosed, the screening measurements will be the baseline. If an assessment has both a date and time that exactly match the date and time of first dose of study drug, the assessment will be counted as baseline.
    - Baseline pathogens however will include any pathogens identified from samples during the baseline/screening visit. If no pathogens are identified from these samples, then a Day 2 or 3 ABSSSI site sample can be used as baseline if the sample is considered acceptable.
    - In the event of missing baseline lesion measurements, a lesion size baseline measurement may include a measurement up to 6 hours after the first dose.
- Change from baseline - Change from baseline will be calculated for each subject at the specified time point as the value at the specified time point minus that subject's baseline value.
- Study day – For a given date (date), the study day is calculated as days since the date of first dose of study drug (firstdose).

  Study day = date – firstdose + 1, where date ≥ firstdose
  Study day = date – firstdose, where date < firstdose
- Days – Durations, expressed in days, between one date (date1) and another later date (date2) are calculated using the following formula: duration in days = (date2-date1+1).

- Body Mass Index (BMI) - BMI (kg/m^2) = weight (kg) / [[height (cm)/100]^2].
- Age, in years, will be computed as from the date of informed consent and the date of birth.

9.5 Handling of Missing Data

All missing data and missing and partial dates for events occurring after randomization or for medications received after randomization will be queried for a value. If no value can be obtained missing data will be handled as outlined below:

All AEs with partial or missing dates and times will be considered treatment emergent unless a partial start date and/or time indicates the AE began prior to the start of study medication or a stop date indicates the AE ended prior to the start of study medication.

The severity and causality assessment for adverse events should not be missing and will be queried for a value. Should there be missing data, adverse events with missing severity will be considered severe and adverse events with missing relationship to study drug will be considered related to study drug.

Missing start and stop times for 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 study drug, 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 study drug, 00:01 will be used for end time. The actual value (blank) will be recorded on the e-CRF and will be used in the listings.

All other (non-antibiotic) medications with partial or missing dates and times recorded on the concomitant medication eCRF will be considered concomitant unless a partial stop date and time clearly indicates it was stopped before the first dose of study treatment.

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

- For the primary efficacy outcome measure (early clinical response at 48 to 72 hours):
- The subject will have missing data if there is no lesion size measurement (either length or width) at the EA visit and will be defined as an indeterminate response.
- If the time of administration of the first dose of study drug is missing, the subject will also be defined as an indeterminate response.

For the Investigator's assessment of clinical response:

- Subjects will be defined as an indeterminate if the Investigator cannot determine whether the subject is a clinical success or failure or if any data is missing to make a determination of failure or success. By definition, subjects with an indeterminate response are included in the denominator for analyses in the ITT, MITT, and micro-ITT analysis sets, and thus, are considered failures; however subjects with an indeterminate response are excluded from the CE-EOT, CE-PTE, and ME 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; hence a per-pathogen microbiological response will be considered missing or indeterminate only if the clinical response is also missing or 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 (i.e., only subjects with available data will be included in the denominators).

9.6 Comments on Statistical Analysis

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

- All listings will be sorted by subject number in ascending order. All relevant data captured on the case report forms (eCRFs) and external data sources, including specific descriptions of 'other' and comments fields will be included on the listings.
- All summary tables will be presented by study drug. Summary tables presenting results by study visit will include all scheduled study visits using informative visit labels.
- Continuous variables will be summarized using number (n), mean, standard deviation (SD), median, minimum, and maximum. Summaries of blood concentration will also include the geometric mean (GM) and coefficient of variation (CV).
- Frequency counts and percentages will be reported for all categorical data.

- Duration variables will be calculated using the general formula (end date - start date) +1.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., 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.
- For all "by visit" safety tables (e.g., laboratory values, vital signs, ECGs), nominal visits will be summarized. In addition within tables that summarize changes from baseline, the minimum and maximum post-baseline values will be summarized to take unscheduled visits into account.
- Version 9.4 (or higher) of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses performed subsequent to this will be considered post-hoc and exploratory. Post-hoc analyses will be labeled as such on the output and identified in the CSR.

Sensitivity analysis to address potential unblinding event: Any subjects for whom the blind may have been comprised will be examined further using sensitivity analyses. Additional details will be provided in the CSR. These analyses may include tabulations of adverse events, Programmatic Clinical Response at EA, and Overall assessment of clinical response at the PTE visit and these will be repeated with and without these subjects to assess any bias.

10 Statistical Analyses

10.1 Subject Disposition

The number and percentage of subjects included in each of the analysis populations (ITT, MITT, Safety, Micro-ITT, CE-EOT, CE-PTE, ME) will be summarized by treatment group and the number of subjects screened and the reasons for screen failures will also be

summarized. A table will summarize the reasons for exclusion from each population and a listing will be provided that indicates each subject's inclusion/exclusion from the analysis population and the reason for exclusion from each analysis population.

The number and percentage of subjects completing the study, prematurely discontinuing from study drug, and prematurely withdrawing from the study will be presented for each treatment group for the ITT, Safety, and CE- PTE populations. Reasons for premature discontinuation of study drug and/or premature withdrawal from the study as recorded on the e-CRF will be summarized (number and percentage) by treatment group.

A listing of all subjects who prematurely discontinued from study drug or prematurely withdrew from the study will be presented, and the primary reason for discontinuation of study drug or withdrawal from the study will be provided.

10.2 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be presented by treatment group in the ITT, Safety, Micro-ITT, and CE- PTE analysis populations. A table will present the subject demographics (e.g., gender, age, ethnicity and race) and baseline characteristics (height, weight, and BMI) collected before the start of study drug.

A demographic data listing, which includes the date the informed consent was signed, will also be provided.

10.3 Medical and Surgical History

Medical history will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) classification, version 21.1. Medical history (skin infection related) and all other medical history and surgical history will be summarized separately for the ITT Population and Safety population by system organ class, preferred term, and treatment group. Subjects reporting the same system organ class or preferred term more than once will be counted only once for that system organ class and preferred term. Relevant medical and surgical history for all prior and concurrent skin infections, previous history of ABSSSI (within 10 years), current or recent IV drug use, chronic hepatic disease, concurrent secondary infection, history of diabetes mellitus, peripheral vascular disease or alcohol abuse will be identified if possible from the medical history terms and will be summarized treatment group for the ITT and Safety populations.

A listing of medical and surgical history will be provided.

10.4 Baseline Disease Characteristics

The primary disease diagnosis at baseline (cellulitis/erysipelas, wound infection, or major cutaneous abscess), location of infection, symptoms of infection, and size of infection (<=300 cm^2, >300-600 cm^2, >600-1000 cm^2 and >1000 cm^2) will be summarized by treatment group for the ITT, Micro-ITT, and CE-PTE Populations. The location of infection will be categorized as follows: head or face or neck, chest or shoulder or back or abdomen, groin or buttock, arm or hand (upper extremities), and leg or thigh or knee or lower leg or ankle or foot (lower extremities).

Baseline information about each ABSSSI including mean infection area, mean infection area by disease diagnosis, and the signs and symptoms of disease will be summarized by treatment group for the ITT, Safety, and CE-PTE populations.

10.5 Baseline Microbiology

The number and percentage of subjects with each type of ABSSSI site specimen obtained, whether or not there was Gram stain, whether there was growth, whether there was culture grown, and the number of unique pathogens from the local laboratory will be provided by treatment group in the Micro-ITT and ME populations. Baseline blood specimen results from the local laboratory will be summarized similarly for the Micro-ITT and ME populations. All ABSSSI site specimen and blood specimen Gram stain results will be listed.

The pathogenic organisms identified by the central laboratory from the baseline blood culture or culture of the ABSSSI specimen will be presented. The number and percentage of subjects with Gram positive and Gram negative organisms will be presented by genus and species for the Micro-ITT and ME populations overall and by infection type. The same pathogen identified from both the blood and the ABSSSI culture will be counted only once in the summary. The pathogenic organisms identified at baseline from blood sample(s) will also be presented for the Micro-ITT and ME populations.

The number and percentage of subjects with monomicrobial Gram-positive, polymicrobial Gram-positive, mixed (Gram positive and Gram negative) infections, will be presented by treatment group, and provided for specimens from blood or ABSSSI culture for both the Micro-ITT and ME populations. When per-subject counts of *S. aureus* are presented, subjects with both MRSA and MSSA are counted only once.

A listing will be provided that includes all baseline and post-baseline isolates obtained from the blood and primary ABSSSI site specimen and will indicate the type of specimen and pathogenic organism identified from both the local and central laboratories. Gram stain results will also be listed.

The minimum inhibitory concentration (MIC) of contezolid acefomacil to baseline pathogens from the primary ABSSSI site or blood culture will be summarized by genus, species and treatment group in the Micro-ITT and ME populations. The MIC of linezolid will be summarized similarly.

Summary Statistics (range, MIC50, MIC90) will be presented for the study drug received to baseline pathogens from the primary ABSSSI site or blood culture will be summarized by treatment group in the Micro-ITT and ME populations. MIC50 and MIC90 values will only be presented for a particular pathogen if there are >=10 pathogens identified within a treatment arm. The MIC50 and MIC90 are the MICs required to inhibit the growth of 50% and 90% of organisms, respectively. For subjects with more than one baseline pathogen of the same genus and species, the one with the highest MIC to study drug received will be selected for analysis; thus subjects are counted only once for that pathogen. If there is a tie, the MIC with the lowest disk diffusion (if applicable) to study drug received will be chosen. Otherwise, the highest accession number is chosen.

10.6 Prior and Concomitant Medications

All prescription medications and over-the-counter medications, including herbal, nutritional, and dietary supplements (e.g., any antacid, iron supplement, or multivitamin) administered within 2 weeks (14 days) prior to randomization and during the study between Day 1 and EOT will be documented in the eCRF.

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Generic Drug Names using the World Health Organization (WHODrug March/Sep 2018) dictionary. Anatomical Therapeutic Chemical Classification (ATC) level 4 (fourth level indicates the chemical/therapeutic/pharmacologic subgroup) and 3 (third level indicates the therapeutic/pharmacologic subgroup).

Prior medications are those medications taken before the first dose of study drug. Concomitant medications are those medications taken at the start of study drug or initiated after the initial dose of study drug, or medications that were initiated prior to the start of

study drug and continue to be taken after study drug is administered. (See the "Handling of Missing Data" section for details on handling in the event of missing medication dates.)

The proportion of subjects who receive the following prior and concomitant medications will be summarized ATC level 3 class, preferred term, and treatment group:

- Prior systemic or topical antibacterial medications taken prior to the first dose of study drug (ITT, and CE-PTE populations)
- Concomitant systemic or topical antibacterial medications (excluding study drug) taken between time of the first administration of study drug on Day 1 and the EOT Visit (ITT, CE-EOT populations) and the PTE Visit (ITT, CE-PTE)
- Prior non-antibacterial medications taken (ITT, Safety populations)
- Concomitant non-antibacterial medications (ITT, Safety Population)

Subjects will be counted only once for an ATC class and preferred term.

Receipt of systemic and topical antibacterial medications in the 96 hours prior to Dose 1 of study drug is an exclusion criterion. However, a listing will be provided of all antibacterial medications received in this time frame, and the reason for receiving, should subjects be enrolled having met this exclusion criterion.

10.7 Study Drug Exposure and Compliance

The active study drugs are contezolid acefosamil (IV and PO) and linezolid (IV and PO), which will be administered for a total of 10 to 14 days. Subjects may receive the IV formulations for the entire treatment duration or be switched to the PO formulations (after receiving at least 3 IV doses) to complete 10 to 14 days of treatment. All subjects will start with IV therapy, with either contezolid acefosamil 1500 mg IV x 1 dose followed by 1000 mg IV q12h (± 2 hours) or linezolid 600 mg IV q12h (± 2 hours), and all subjects will receive at least 3 total doses of IV study drug. For subjects who switch from IV to PO treatment, 2 contezolid acefosamil capsules (each capsule containing 650 mg of contezolid acefosamil for a total of 1300 mg) or 2 linezolid capsules (each capsule containing 300 mg of linezolid for a total of 600 mg) will be administered PO q12h [± 2 hours]) to complete a total of 10 to 14 days of treatment.

By treatment group summaries will be provided for total number of doses, number of IV doses, and the number of PO doses in the ITT, Safety, and CE-PTE populations.

Duration of treatment is defined as the number of calendar days from when the subject first received study treatment until the day that they last received study treatment (IV or PO) and is calculated as (date of last dose – date of first dose +1).

Compliance to study drug will be calculated based on the total number of doses taken, divided by the total number of expected doses, in the time period between the dates of the first and last doses of study drug.

$$\boldsymbol{Compliance} = 100 * \frac{(Number\ of\ doses\ received\ (IV\ or\ PO))}{(Expected\ number\ of\ doses\ (IV\ or\ PO))}$$

Descriptive statistics of percent compliance as well as the number and percentage of subjects at least 80% compliant by number of doses (IV or PO), will be provided by treatment group for the ITT, Safety, and CE-PTE populations.

Descriptive statistics of study drug exposure by route of administration will also summarized by treatment group, for the ITT and Safety and CE-PTE populations.

10.8 Efficacy Analyses

For all efficacy analyses, subjects will be analyzed in the group to which they were randomized. By definition, subjects who receive the wrong study drug are not included in the CE and ME populations. The primary and secondary efficacy analyses are identified in Table 9.

Table 9: Efficacy Analyses

	Efficacy Populations					
	ITT	**MITT**	**micro-ITT**	**CE-EOT**	**CE-PTE**	**ME**
Primary:						
Early clinical response at EA	√					
Secondary:						
Early clinical response at EA		√				
Early clinical response at EA (overall and by baseline pathogen)			√			
Percent reduction in lesion size at Day 7	√	√				
Investigator's assessment of clinical response at EOT	√	√		√		
Investigator's assessment of clinical response at PTE and LFU	√	√			√	
Per-subject microbiological response at PTE			√			√
Per-pathogen microbiological response at PTE			√			√
Investigators assessment of clinical response at PTE and LFU (overall and by baseline pathogen)			√			√
CACO	√		√		√	

CACO = composite assessment of clinical outcome (combined outcome of early clinical response at EA and Investigator's assessment of clinical response at PTE); CE = clinically evaluable; EA = early assessment; EOT = end of therapy; ITT = intent-to-treat; LFU = late follow-up; ME = microbiologically evaluable; MITT = modified intent-to-treat; micro-ITT = microbiological intent-to-treat; PTE = post therapy evaluation

10.8.1 Primary Efficacy Analysis

The primary efficacy analysis is an examination of the percentage of responders in the contezolid acefosamil treated group vs. the percentage of responders in the linezolid group at EA in the ITT population. This aligns with the FDA's primary efficacy endpoint of interest in ABSSSI studies (reference 1). The number and percentage of responders, non-responders and indeterminate responses will be summarized by treatment group and an exact 95% CI will be provided for the responder rates in each treatment group. The difference between the responder rates will be calculated and 95% CI for the difference between response rates will be calculated using a Wald continuity correction. A summary of reasons for programmatic clinical failure and indeterminate response at the EA Visit will

also be provided. The reasons for failure and indeterminate will be summarized as well for the programmatic clinical response at EA in the ITT population.

10.8.2 Secondary Efficacy Analysis

Secondary efficacy analyses will include the following: early clinical response at EA in the MITT population, early clinical response at the EA visit by baseline pathogen and treatment group in the micro-ITT population and changes from baseline in the percent reduction in lesion area at Day 7 summarized in a continuous and categorical manner (≤10%, >10-20%, >20-50%, >50-75%, >75%), by treatment group in the ITT and MITT populations.

The Investigator's assessment of clinical response will be classified as described in sections 8.1.2 and 8.1.3. The number of subjects with an Investigator's assessment of clinical success, clinical failure, and indeterminate at EOT will be summarized for both treatment groups in the ITT, MITT and CE-EOT populations. Similarly, the Overall Assessment of Clinical Response based on the Investigator's assessment at PTE and the Investigator's assessment at LFU will also be summarized for both treatment groups in the ITT, MITT and CE-PTE populations.

Note that, by definition, subjects with an indeterminate response will be excluded from summaries in the CE-EOT and CE-PTE populations. The 95% CI will be provided for the rate of clinical success for each treatment group. The 95% CI will also be provided for the difference in rates of success at EOT in the ITT and the CE-EOT populations. Similarly the 95% CI will be provided for the difference in rates of success at PTE in the ITT and the CE-PTE populations. The reasons for failure and indeterminate will be summarized as well for the clinical responses at EOT and PTE for the indicated populations as well as for the ITT and MITT populations.

The Overall Assessment of Clinical Response based on the Investigator's assessment at PTE and the Investigator's assessment at LFU will also be summarized by baseline pathogen in the Micro-ITT and ME populations. The Overall Assessment of Clinical response at PTE will also be summarized by the MIC of Linezolid and MIC of Contezolid Acefomacil by treatment group in the Micro-ITT and ME populations.

The durability of clinical response (rate of sustained clinical response and clinical relapse/failure and indeterminate) at LFU will be summarized by treatment group in the ITT, MITT and ME populations.

The rates of success as assessed by the CACO as described in Section 8.1.5 will be summarized in the ITT, micro-ITT, and CE-PTE populations.

10.8.3 Additional Efficacy Analysis

Early clinical response at the EA visit will also be summarized by ABSSSI type in the ITT and MITT populations. Also early clinical response at EA will be summarized by pathogen and baseline MIC of contezolid acefosamil and linezolid, by treatment in the Micro-ITT and ME populations.

Overall assessment of clinical response at PTE will also be summarized by ABSSSI type in the ITT, MITT and CE-PTE populations. Also the overall assessment of clinical response at PTE will be summarized by pathogen and baseline MIC of contezolid acefosamil and linezolid, by treatment in the Micro-ITT and ME populations.

10.8.4 Microbiological Outcomes

The number and percentage of subjects with favorable, unfavorable, and indeterminate microbiological responses will be summarized at PTE in the micro-ITT and ME populations. A 2-sided exact 95% CI will be constructed for the percentage of subjects with favorable response and a 95% CI will be calculated for the difference in the per-subject favorable microbiological response using a Wald continuity correction.

Microbiologic response will be summarized by baseline pathogen and treatment at the PTE visit for each pathogen isolated at baseline from the primary ABSSSI site or from blood in the micro-ITT and ME populations.

A listing will be provided that presents the subjects with a superinfection or a new infection.

10.9 Safety Analyses

All safety analyses will be conducted in the Safety population.

10.9.1 Adverse Events

Verbatim descriptions of AEs will be coded using Version 21.1 of MedDRA. Summary tables will be provided for all treatment-emergent adverse events (TEAEs). A treatment-emergent AE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug and up through the last study visit or evaluation, or an SAE that occurs during or after the first administration of study drug up through 30 days after the final administration of study drug.

An overall summary of AEs will include number and percentage of subjects in each treatment group who experienced at least one AE of the following categories: any AE, any TEAE, any drug-related TEAE (defined as possibly, probably or definitely related to study drug), any severe or life-threatening TEAE, any serious TEAE (SAE), any drug-related SAE, any SAE leading to death, and any TEAE leading to premature discontinuation of study drug and any SAE leading to premature study drug discontinuation.

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/life-threatening/death); and by system organ class, preferred term, and relationship (unrelated [defined as unrelated or unlikely related to study drug] or related to study drug). In addition, all TEAEs will also be summarized by system organ class and preferred term separately based on whether the TEAE started while the subject received IV or oral study drug (select AE tables only).

Summary tables will be presented alphabetically by system organ class and preferred term within system organ class. 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 study drug.

The number and percentage of subjects reporting a SAE and reporting a TEAE leading to premature discontinuation of study drug in each treatment group will be summarized by system organ class and preferred term.

The incidence of TEAEs that occur in at least 2% of subjects in either treatment group will be summarized by preferred term and treatment group, sorted by decreasing frequency in the contezolid acefosamil group.

In addition, all AEs (including non-TEAEs), serious AEs (SAEs) , and TEAEs leading to study drug discontinuation will be provided in listings. AEs of special interest will also be summarized by treatment groups.

10.9.2 Laboratory Values

Summaries of laboratory data will include hematology, chemistry, coagulation and C-reactive protein laboratory 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 10.

Table 10: Laboratory Parameters

Renal	Creatinine Blood urea nitrogen
Liver	Alkaline phosphatase ALT AST Bilirubin direct Bilirubin total GGT LDH
Electrolytes	Bicarbonate Calcium Chloride Magnesium Potassium Sodium
Other	Albumin Cholesterol (total) Creatine kinase Glucose, nonfasting Phosphorus Total protein Uric acid

Several analyses of the laboratory data will be presented. Descriptive statistics (based on SI units) for chemistry, hematology, and coagulation values and the change from baseline will be summarized by treatment group at Day 1, EA, Day 7, EOT, and PTE visits, and for the

overall minimum and maximum post-baseline values (which includes unscheduled visits). 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.

For subjects with missing central laboratory results at baseline, the local baseline results will be used after transformation to centralized local baseline results. On a per laboratory test basis, the local baseline result will be normalized using the local laboratory range. The normalized local baseline result will be converted to a centralized local baseline result using the range for the central laboratory test. This transformation (Normalization and Centralization) is defined as follows, where NRL is the Normal Range Low and NRH is the Normal Range High:

Normalized Local Baseline Result =

(Local Baseline Result – Local NRL) / (Local NRH – Local NRL)

Centralized Local Baseline Result =

*Normalized Local Baseline Result * (Central NRH – Central NRL) + Central NRL*

Toxicity grade will be determined based on the modified DMID criteria (Appendix B). Shift tables will be presented to show the number of subjects with a chemistry or hematology laboratory value with a grade of 1, 2, 3 or 4 at baseline versus the worst post-baseline value.

Post-baseline substantially abnormal clinical laboratory values will also be summarized. For hematology, where substantially abnormal is defined as <75% of the lower limit of normal (LLN) (<50% of ANC) for values normal at baseline, and <75% of the LLN (<50% for ANC) and of baseline for values abnormal at baseline. For chemistry substantially abnormal is defined as 2 x the ULN for values normal at baseline and 2 x the ULN and 2 x the baseline.

The number and percentage of subjects with elevated liver function assessments will also be summarized by visit using the following categories: >3-5 xULN, >5-10 xULN, and >10 xULN, where ULN is the upper limit of normal.

A listing will be presented identifying all subject records meeting the substantially abnormal hematology, chemistry criteria. This same listing will also contain any abnormal liver function records that meet Hy's law criteria, which is: AST or ALT > 3xULN, alkaline phosphatase <=2xULN, and total bilirubin >1.5xULN.

A general detailed subject listing of all laboratory data collected during the study will be provided. 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).

10.9.3 Vital Signs

Blood pressure (systolic and diastolic), respiration rate, heart rate, and temperature will be summarized using descriptive statistics by treatment group at each time point at which they were measured. Descriptive statistics of the change from baseline to each post-baseline time visit will also be provided.

The number and percentage of subject abnormal values, identified by the threshold levels provided in Table 11, will be summarized by treatment group. Only subjects with both baseline and post-baseline values will be summarized for diastolic blood pressure increases

Table 11: Abnormal Vital Threshold Values

Vital Sign	Threshold
Diastolic blood pressure	> 20 mmHg increase from baseline
Systolic blood pressure	≥ 140 mmHg
Heart rate	< 60 beats/min
Heart rate	> 120 beats/min
Temperature	>102.3 F

All vital signs will also be provided in by-subject listings.

10.9.4 Electrocardiogram

ECGs will be recorded in triplicate at each visit, where all three measurements are taken within a 15 minute period. The mean of available triplicate values will be calculated and reported for each time point. If there are no triplicate values, the mean of the duplicate or single value will be used. Descriptive statistics for central ECG parameters of RR interval, PR interval, QRS duration, QT interval, and QTcF interval, as well as the changes from baseline will be presented by treatment group at each scheduled visit.

For centrally collected QTcF values, a distribution showing counts and percentages for the maximum increase post-baseline to EOT will be provided using the following categories: <0, ≥1 - <30 msec, ≥30 - <60 msec, ≥60 - <90 msec, >=90 msec. Actual QTcF visit values will also be summarized using counts and percentages for the following categories: ≤ 450, > 450 - ≤ 480, >480 - ≤ 500, and >500 msec).

A listing of central and local electrocardiogram data will also be provided and will include the tracing results of normal, abnormal and clinically significant status for these measurements.

10.9.5 Physical Examinations

Physical examination results will be presented in by-subject listings.

10.9.6 Basic Ophthalmoscopy Exams and Visual Fields

Descriptive statistics for basic ophthalmoscopy and visual field parameters at baseline and EOT visit will be presented by treatment group. Snellen visual acuity scores will be categorized as identified in the Table 12 below. A summary table of this visual acuity score data will be created that includes the number and percentage of subjects in each treatment group with the following Snellen vision category changes from baseline to each visit:

- Improvement or no change in both eyes
- Improvement in one eye and worsening by 1 Snellen category in the other eye
- Improvement in one eye and worsening by 2 or more Snellen categories in the other eye
- Worsening by 1 Snellen category in both eyes
- Worsening by 1 Snellen category in one eye and worsening by 2 or more Snellen categories in the other eye
- Worsening by 2 or more Snellen categories in both eyes

If subjects require corrective eyewear for vision, then only subjects who did not wear corrective eyewear for both visits or who did wear corrective eyewear for both visits will be included in summary tables. Baseline is defined as the Snellen measurement prior to the first dose of study drug.

Table 12: Ranges of Visual Acuity Loss

Vision Category	Snellen Decimal	**Examples of possible Snellen Ratios**
Normal Vision	≥0.8	20/12, 20/15, 20/20, 20/25
Near-Normal Vision	<0.8 and ≥0.32	20/30, 20/40, 20/60
Moderate Low Vision	<0.32 and ≥0.125	20/70, 20/80, 20/100
Severe Low Vision	<0.125 and ≥0.05	20/200, 20/400
Profound Low Vision or Worse than Profound Low Vision	<0.05	NA

Note: All Snellen ratios will be converted to "Snellen Decimals." For example, 20/12=1.67 and 20/15=1.33. These categories of vision loss are definedbased on as report prepared for the International Council of Opthalmology (See reference 2).

All Snellen examination scores, basic ophthalmoscopy exams, and visual field data will be provided in a by-subject listing.

10.9.7 Pharmacokinetic Analyses

These will not be summarized or listed here, as the PK analysis and related deliverables for plasma concentrations, metabolite concentrations, and PK parameters, will be produced by a different vendor.

10.9.8 Protocol Deviations

A listing of all protocol deviations will be provided. Protocol deviations will also be reviewed by the Sponsor and categorized into general categories such as:

- Eligibility criteria not met
- Study drug administration error
- Randomization error

- Non-compliant visit schedule
- Non-compliant study procedure
- Non-compliant informed consent process
- Other

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 (or important) deviation, and the number of subjects with at least one deviation in each category will be presented by treatment group for the ITT Population. A major (or important) deviation is defined as one that potentially affects the efficacy and/or safety analyses and will be determined by a review by the Sponsor.

11 Deviations from the Protocol

The SAP and the population definition sections of the protocol specify that the Clinically Evaluable populations include subjects who "did not receive any potentially-effective systemic antibacterial therapies other than protocol specified study drug(s) between Day 1 and timepoint for assessment (except for adjunctive aztreonam or in cases of treatment failure)…"; however Figure 2 of the protocol incorrectly omits inclusion of the word "potentially".

The protocol EA visit window is 48-72 hours (after the first dose of study drug), but the window is extended to the lower bound of 46 hours.

12 Reference List

1. Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry - Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. Oct 2013. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071185.pdf

2. Visual Standards-Aspects and Ranges of Vision Loss with Emphasis on Population Surveys. Report prepared for International Council of Ophthalmology at the 29th International Congress of Ophthalmology Sydney, Australia, April 2002. (http://www.icoph.org/downloads/visualstandardsreport.pdf)

Appendix A) Schedule of Events

The calendar day on which the first dose of study drug is administered is Day 1.

Procedure or Assessment	Screening/ Baseline[1] (≤ 24 hrs of first dose)	Study Treatment Period					PTE[5]	LFU[6]
		Day 1[2]	Day 2	EA[3] (48-72 hours)	Day 7 (± 1 day)	EOT[4] (+ 1 day)	7-14 Days After EOT	21-28 Days After EOT
Informed consent[7]	X							
Medical/surgical history	X							
Prior and concomitant therapy[8]	X	X	X	X	X	X	X	X
Examination, measurement, and signs and symptoms of ABSSSI[9]	X[10]			X	X	X	X	
Document primary ABSSSI lesion by digital photography[11]	X[10]			X	X	X		
Investigator's assessment of clinical response						X	X	X
Activity assessment[12]	X					X	X	X
Complete physical examination[13]	X[10]					X		
Focused physical examination[14]				X	X		X	
Vital signs[15]	X[10]			X	X	X	X	
12-Lead ECG[16]	X[10]	X[17]		X		X	X	
Height and weight	X							
Adverse events[18]	X	X	X	X	X	X	X	X
Laboratory tests[19]	X[10]			X	X	X	X	
Serology tests [20]	X							

Procedure or Assessment	Screening/ Baseline[1] (≤ 24 hrs of first dose)	Study Treatment Period					PTE[5]	LFU[6]
		Day 1[2]	Day 2	EA[3] (48-72 hours)	Day 7 (± 1 day)	EOT[4] (+ 1 day)	7-14 Days After EOT	21-28 Days After EOT
Pregnancy test[21]	X[10]					X		
Estimate CrCl[22]	X							
PK samples[23]		X	X			X		
ABSSSI specimen Gram stain and culture[24]	X[10]			X	X	X	X	
Blood cultures[25]	X[10]			X	X	X	X	
Randomization[26]		X						
Administration of study drug (10 to 14 days)[27]		X	X	X	X	X		

ABSSSI = acute bacterial skin and skin structure infection; β–HCG = beta-human chorionic gonadotropin; CrCl = creatinine clearance; CRP = c-reactive protein; EA = early assessment; ECG = electrocardiogram; EOT = end of therapy; eRT = eResearch Technologies; LFU = late follow-up; PK = pharmacokinetic; PTE = post therapy evaluation; UA = urinalysis.

1. Screening/baseline assessments must occur within 24 hours prior to first administration of study drug.
2. Day 1 is the first day of study drug administration; subsequent study days are consecutive calendar days.
3. Perform EA assessments at 48 to 72 hours after the start of the first dose of IV study drug.
4. Perform EOT assessments on the last calendar day of study drug (+ 1 day). Subjects who prematurely discontinue study drug or withdraw from the study should have all EOT assessments performed on the day of discontinuation of study drug or withdrawal from the study (+ 1 day).
5. Perform PTE assessments 7 to 14 days after EOT.
6. Perform LFU assessments 21 to 28 days after EOT. If the subject has improved to the point that they have returned to their usual premorbid activity (work/school), and if the primary site has little or no pain, swelling, redness, or purulent/seropurulent drainage at PTE, the LFU visit may be performed over the telephone.
7. Written informed consent must be obtained prior to initiating any study assessment or procedure.
8. Record all prior medications taken within 2 weeks prior to randomization; record all concomitant medications between Day 1 and EOT, and only concomitant antimicrobial agents and concomitant medications taken for an AE between EOT and LFU.
9. Direct evaluation of signs and symptoms of ABSSSI by the Investigator at EA, Day 7, EOT, and PTE; assessments include manual measurement of the primary ABSSSI lesion size (longest length and perpendicular width) with a ruler provided by the Sponsor (Protocol Section8.1).
10. Procedures that must be repeated on Day 1 prior to dosing if they were collected > 24 hours prior to first administration of study drug.

11. Document the primary ABSSSI lesion via digital photography at screening/baseline, EA, Day 7, and EOT using the digital camera provided by the Sponsor (Protocol Section 8.3).
12. At screening/baseline, record if the subject's premorbid activities (work/school) are compromised. At subsequent visits, record the date the subject returned to premorbid level of activity (work/school), as applicable.
13. Perform a complete physical examination (i.e., general appearance, head, ears, eyes [including basic Snellen visual acuity and visual field testing], nose, throat, dentition, thyroid, chest [heart, lungs], abdomen, skin/soft tissues, neurological, extremities, back, neck, musculoskeletal, lymph nodes) at screening/baseline and EOT.
14. Perform a limited, symptom directed physical examination as clinically indicated at EA, Day 7, and PTE.
15. Record vital signs (heart rate, blood pressure, respiratory rate, and temperature) at screening/baseline, EA, Day 7, EOT, and PTE. If > 1 temperature is measured within a calendar day, record the highest daily temperature measured. Vital signs will be collected prior to collection of blood laboratory samples. Oral or rectal temperatures are acceptable; the site of measurement will be collected in the eCRF.
16. Obtain triplicate ECGs within a 15-minute period, each separated by at least 1 minute, at screening/baseline, Day 1 (predose and postdose), EA, EOT, and PTE. ECGs will be collected prior to collection of blood laboratory (including PK) samples. The time of prior dose of study drug and relationship of time of ECG to dose must be documented All ECGs will be performed on ECG machines provided by eRT and will be sent to eRT for central reading.
17. Within 1 hour prior to start of IV infusion (unless screening/baseline ECG is performed in triplicate and is within 1 hour prior to start of IV infusion) and another within 2 hours after completion of IV infusion.
18. Adverse events are collected between written informed consent and LFU. During the LFU phone call, symptoms related to possible relapse of ABSSSI will be evaluated as part of the safety assessment.
19. Perform safety laboratory tests, including hematology, chemistry, and coagulation tests, UA, and CRP, at screening/baseline, EA, Day 7, EOT, and PTE. Include urine microscopy if UA is positive for red blood cells, WBCs, or protein (Protocol Appendix 4). Samples for screening/baseline tests will be drawn and sent to local laboratory (to confirm eligibility) and central laboratory. All subsequent laboratory tests will be drawn and sent to the central laboratory.
20. Serology tests include Anti-HBcAg anti-HBsAg, HBsAg, HCV Ab, HIV Ab (Protocol Appendix 4)
21. Females of childbearing potential up to 2 years postmenopause must have a serum or urine β–HCG pregnancy test at baseline and EOT (otherwise, females must be surgically sterile, i.e., have had a tubal ligation, hysterectomy, or bilateral oophorectomy). Male and female subjects must agree to comply with using a highly effective form of birth control (see Protocol Section 10.3 from baseline through LFU. If the pregnancy test is positive at the EOT visit, or if a female partner of a male subject becomes pregnant, follow the reporting requirements in Protocol Section 10.3.
22. Calculate estimated CrCl using screening/baseline height (m), actual weight (kg), and serum creatinine (Protocol Section 7.1).
23. Obtain PK samples as follows (Protocol Section 11):
    - One sample after 1st IV dose, between 0.5 to 2 hrs after the end of the 1st infusion;
    - Three samples with the 3rd IV dose: obtain a 1st blood sample within 2 hours before the 3rd IV dose (trough level), a 2nd blood sample between 0.5 and 3 hours after the end of the 3rd IV dose,and a 3rd blood sample between 4 and 11 hours after the end of 3rd IV dose, but before the 4th dose (IV or PO);
    - Three samples at EOT: obtain 1 blood sample within 2 hours before the last dose (IV or PO). If the last dose is given PO: obtain 1 blood sample between 1.5 to 4 hours after the last dose and obtain 1 additional sample between 5 to 12 hours after the last dose. If the last dose is given IV: obtain 1 blood sample between 0.5 and 3 hours after the end of the last infusion and obtain 1 additional sample between 4 and 11 hours after the end of the last infusion.
24. Obtain appropriate ABSSSI site specimen from all subjects at screening/baseline, and perform Gram stain and culture at the local laboratory (Protocol Section 8.2**Error! Reference source not found.**). The ABSSSI site specimen should be obtained before administration of antibacterial therapy whenever possible. Repeat post-screening/baseline ABSSSI specimen culture and Gram stain at subsequent visits only if clinically indicated (e.g., the subject is deemed a clinical failure or if purulence and discharge from the ABSSSI site continues after screening/baseline).

25. Two sets of blood cultures (each set consists 1 aerobic and 1 anaerobic blood culture bottle from 2 separate venipuncture sites) will be collected from all subjects, regardless of location of management (inpatient or outpatient) (Protocol Section 8.2). The blood cultures should be obtained before administration of antibacterial therapy, whenever possible. Blood cultures must be repeated every 3 days (± 1 day) if the previous blood culture was positive, or at any time after screening/baseline if clinically indicated.
26. Verify that the subject meets all study inclusion and exclusion criteria before randomization on Day 1.
27. Subjects receive study drug q12h (± 2 hours) for 10-14 days. On Day 1, the first dose of study drug should be administered as quickly as possible after eligibility criteria are met. Subjects will receive the first 3 doses of study drug intravenously and then may switch to oral study drug if the primary ABSSSI lesion has not increased in area from the screening/baseline assessment and the Investigator determines that the subject has sufficient PO intake of food and drink to safely support the administration of PO doses of antibiotics.

Appendix B) Division of Microbiology and Infectious Diseases Adult Toxicity Table

The DMID Adult Toxicity Table (November 21, 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. 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.

ENZYMES					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	<1.25xULN	1.1-2.0xULN	2.0-3.0xULN	3.0-8.0xULN	>8.0xULN
ALT (SGPT)	<1.25xULN	1.1-2.0xULN	2.0-3.0xULN	3.0-8.0xULN	>8.0xULN
GGT	<1.25xULN	1.1-2.0xULN	2.0-3.0xULN	3.0-8.0xULN	>8.0xULN
Alkaline Phosphatase	<1.25xULN	1.1-2.0xULN	2.0-3.0xULN	3.0-8.0xULN	>8.0xULN

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
% Polymorphonuclear Leucocytes + Band Cells	≤80%	>80%-90%	>90–95%	>95%	----------

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 no prior 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	11.6-1.5	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 (when accompanied by any increase in other liver function test)	<1.1xULN	1.1 - <1.25xULN	1.25 - <1.5xULN	1.5 – 1.75xULN	> 1.75xULN
Hyperbilirubinemia (when other liver function are in the normal range)	<1.1xULN	1.1 - <1.5xULN	1.5 - <2.0xULN	2.0 – 3.0xULN	> 3.0xULN
BUN	<1.25xULN	1.25-2.5xULN	2.6-5xULN	5.1-10xULN	>10xULN
Hyperuricemia (uric acid) (mg/dL)	<7.5	7.5–10.0	10.1–12.0	12.1–15.0	>15.0
Creatinine	<1.1xULN	1.1-1.5xULN	1.6-3.0xULN	3.1-6xULN	>6xULN

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

Appendix C) Safety Laboratory Tests

Hematology:

- Hemoglobin
- Hematocrit
- Erythrocyte count
- Leukocyte count (WBCs)
- Neutrophils
- Lymphocytes
- Monocytes
    - Eosinophils
    - Basophils
    - Platelets

Coagulation:

- Prothrombin time/International normalized ratio (PT/INR)
- Partial thromboplastin time
- Activated partial thromboplastin time (aPTT)

Urinalysis:

- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Occult blood
- Nitrites
- Urobilinogen
- Leukocyte esterase

Urine Microscopy:[a]

- WBCs
- Red blood cells
- Casts
- Bacteria
- Crystals

Chemistry (Serum Concentrations):

- Glucose
- Calcium
- Albumin
- Total protein
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Urea nitrogen
- Creatinine
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Total and direct bilirubin
- Magnesium
- Lactate dehydrogenase
- Phosphorus
- Uric Acid
- Creatine kinase
- Gamma-glutamyl transferase
- Indirect bilirubin
- Cholesterol
- Triglycerides
- β-Human chorionic gonadotropin for females
- C-reactive protein (CRP)

SCREENING/BASELINE ONLY:

- Creatinine clearance
- Anti-HBcAg (anti-hepatitis B core antigen)
- Anti-HBsAg (anti-hepatitis B surface antigen)
- HBsAg (hepatitis B surface antigen)
- HCV Ab (hepatitis C antibody)
- HIV Ab (human immunodeficiency virus antibody)

[a] Performed if UA is positive for red blood cells, WBCs, or protein.

Appendix D) Allowed Prior Antibiotics

Allowed Antibiotics (One dose within 96 hours prior to randomization)		**Disallowed Antibiotics**
Penicillins:		
Amoxicillin Amoxicillin-Clavulanate Amoxicillin-Sulbactam Ampicillin Ampicillin-Sulbactam Dicloxacillin	Nafcillin Oxacillin Penicillin-G Penicillin-V Piperacillin Piperacillin-Tazobactam	NONE
Cephalosporins:		
Cefaclor Cefadroxil Cefazolin Cefdinir Cefepime Cefixime Cefditoren Cefotaxime	Cefpodoxime Cefprozil Ceftaroline Ceftazidime Ceftibuten Cefuroxime Cephalexin Loracarbef	Ceftriaxone
Carbapenems:		
Doripenem Imipenem Meropenem		Ertapenem
Glycopeptides:		
Televancin Vancomycin		Dalbavancin Oritavancin
Fluoroquinolones:		
Ciprofloxacin		Levofloxacin Moxifloxacin
Macrolides:		
Clarithromycin Erythromycin		Azithromycin Clarithromycin XL
Tetracyclines:		
Doxycycline Minocycline		Minocycline Extended Release
Miscellaneous:		
Clindamycin Metronidazole Trimethoprim-sulfamethoxazole/Co-trimoxazole		Daptomycin
Oxazolidinones:		
NONE		Linezolid Tedizolid

Appendix E) Local Signs and Symptoms of ABSSSI

Local signs and symptoms will be assessed for the primary ABSSSI site.

The Investigator is to provide a categorical assessment and comparison to baseline of the following parameters using the scale below:

Parameter	Absent	Mild	Moderate	Severe
Erythema	None	Pink	Red	Fiery red
Swelling/edema	None	Swelling just apparent on casual inspection (up to 2 mm of pitting)	Marked swelling (≤ 4 mm of pitting)	Maximal swelling (> 4 mm of pitting)
Localized warmth	None	Slightly warm	Warm	Hot
Tenderness on palpation	None	Slight or mild tolerable discomfort on palpitation	Uncomfortable with light palpitation or pressure	Intolerable by even a mild stimulus such as sheet touching
Drainage	None	Serous	Seropurulent	Purulent
Fluctuance	None	Present	Not applicable	Not applicable
Induration	None	Present	Not applicable	Not applicable