CLINICAL PROTOCOL

Protocol No.	MRX4-201
Title:	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 Phase:	2
Product Name:	Contezolid acefosamil
Indication:	Treatment of patients with acute bacterial skin and skin structure infection (ABSSSI)
Investigators:	Multicenter Study
Sponsor:	MicuRx Pharmaceuticals, Inc. 3916 Trust Way Hayward, CA 94545 Phone: 1-510-782-2021
Sponsor Contact:	Edward Fang, MD SVP, Clinical Development MicuRx Pharmaceuticals, Inc Phone: 415-710-5481 Email: efang@micurx.com
Current Version	Amendment 2
Date	Final, 19 October 2018
Prior Versions:	Original: 16 August 2018 Amendment 1: 27 September 2018

PROTOCOL APPROVAL PAGE

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Personnel Approving Protocol	Signature
Edward Fang, MD SVP, Clinical Development MicuRx Pharmaceuticals, Inc.	
Barry Hafkin, MD EVP, Chief Medical Officer MicuRx Pharmaceuticals, Inc.	

INVESTIGATOR AGREEMENT PAGE

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I have read and I understand protocol MRX4-201 and the Investigator's Brochure. I agree to the following:

1. To conduct the clinical study in compliance with Good Clinical Practice (GCP) and with all applicable regulatory requirement(s), according to the latest version of the protocol agreed to by the Sponsor and given approval/favorable opinion by the IRB

2. To comply with procedures for data recording/reporting

3. To permit monitoring, auditing, and inspection by the Sponsor, its designated representatives, and regulatory authorities

4. To retain the essential documents in the Investigator/institution files until the Sponsor informs me or the institution that these documents are no longer needed

5. To provide copies of the protocol, any subsequent protocol amendments, and all information provided by the Sponsor to the study personnel under my supervision. I will discuss these materials with them in the detail required to ensure that they are fully informed about the investigational drug and the study protocol as appropriate for their study-related responsibilities.

Investigator Signature **Date**

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

Abbreviation	Definition
ABSSSI	Acute bacterial skin and skin structure infection
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}t/0\text{-}12h/0\text{-}24h/0\text{-}\infty}$	Area under the curve vs. time from time zero to last timepoint (e.g., 12 h, 24 h, infinity)
BCS	Biopharmaceutics classification system
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
CACO	Composite assessment of clinical outcome
CE	Clinically evaluable
CI	Confidence interval
C_{max}	Maximum concentration
CNS	Central nervous system
CrCl	Creatinine clearance
CRO	Clinical Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology for Adverse Events
D_5W	5% dextrose in water
DEHP	diethylhexyl phthalate
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web response system
MAOI	Monoamine oxidase inhibitor
MDR	Multidrug-resistant
ME	Microbiologically evaluable
MITT	Modified intent-to-treat
micro-ITT	Microbiological intent-to-treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NS	Normal saline
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Oral
PT	Preferred term
QC	Quality control
QD	Once daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using the Fridericia correction formula
SAE	Serious adverse event
SAER	Serious adverse event report
SAP	Statistical analysis plan
SAR	Suspected adverse reaction

Abbreviation	Definition
SOC	System Organ Class
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
UA	Urinalysis
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
VRE	Vancomycin-resistant enterococci
WBC	White blood cell count

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)
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

1 STUDY SYNOPSIS

Sponsor: MicuRx Pharmaceuticals, Inc.	**Protocol Number:** MRX4-201
Study Drug: Contezolid acefosamil for intravenous (IV) and oral (PO) administration	
Title: 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	
Phase of Development: 2	
Study Site: Approximately 5 to 10 sites in the United States (US)	
Indication: Acute bacterial skin and skin structure infection (ABSSSI)	

Rationale: There is an unmet need for additional antibiotic choices to treat Gram-positive bacterial infections caused by organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).

Contezolid acefosamil (previously referred to as MRX-4), a sodium salt of a contezolid (previously referred to as MRX-1) prodrug, is a synthetic antibiotic in the oxazolidinone class of antimicrobials. Due to the low solubility of contezolid and inability to produce a practical IV formulation using contezolid, an orally bioavailable and water soluble new molecular entity (contezolid acefosamil) was developed, a full battery of preclinical studies was performed, and a successful Phase 1 program was completed.

Contezolid is a novel oxazolidinone with potent in vitro activity against aerobic and anaerobic Gram-positive pathogens, with demonstration of clinical efficacy in ABSSSI in 2 previous Phase 2 studies. Contezolid acefosamil, which rapidly converts to contezolid, is expected to offer similar or more consistent (i.e., improved) pharmacokinetic (PK) properties than other drugs in its class. Contezolid acefosamil will be available in both IV and PO formulations. Therefore, contezolid acefosamil may provide an attractive option to overcome the safety and tolerability challenges with current antibiotic choices in both the hospital and community settings.

Both contezolid and contezolid acefosamil have proven to be highly efficacious in various models of animal infections caused by Gram-positive bacteria, including drug-resistant strains of *S. aureus, Streptococcus pneumoniae*, and enterococci. The animal models used for evaluation included murine sepsis and thigh infection.

This study is designed to evaluate the safety and efficacy of IV and PO administered contezolid acefosamil compared to linezolid in adults with ABSSSI. The primary efficacy endpoint of clinical response at early assessment aligns with the current Food and Drug Administration Guidance for Industry, ABSSSI: Developing Drugs for Treatment (FDA, October 2013).

Study Objectives:

Primary:

- 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

Secondary:

- 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

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.

Screening/baseline assessments for study eligibility will be performed within 24-hours prior to the start of the first dose of study drug. Subjects who provide informed consent, are willing and able to collaborate and cooperate with study protocol requirements and meet all study eligibility criteria will be enrolled and randomized in the study.

Gram stain and culture specimens of the ABSSSI site must 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 cellulitic 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. All ABSSSI site specimens will be processed for Gram stain and culture at the local laboratory, and all blood cultures will be processed at the local laboratory. All bacterial isolates that are identified from an ABSSSI site specimen or blood culture at the local facilities collaborating laboratory will be sent to a designated central laboratory for confirmation of species identification and antimicrobial susceptibility testing. Microbiological methods will be detailed in the Laboratory Manual.

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. If no Gram-negative pathogens are isolated from the screening/baseline cultures by Day 3, aztreonam will be discontinued. Subjects with suspected infections primarily due to anaerobic organisms as the cause for ABSSSI or subjects requiring empiric adjunctive anaerobic antimicrobial coverage are excluded from treatment under this protocol.

Prompt enrollment procedures are encouraged to allow for prompt administration of study drug. 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).

It is expected that most subjects will remain in the hospital or clinic while receiving IV treatment with study drug for a minimum of 3 total IV doses; however, subjects who are clinically stable and have adequate home support with reliable transportation to/from the hospital or clinic may leave and return to the hospital or clinic for IV infusions. Study drug IV infusions are not to be administered at home. Subjects may receive the IV formulation for the entire treatment duration. 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 who are switched from the IV to the PO formulation must remain in the hospital or clinic for observation for at least 90 minutes after the first PO dose and demonstrate good tolerability with the initial dose of PO treatment. 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, EA will be performed 48 to 72 hours after the start of the first dose of IV study drug, EOT will occur on the last calendar day of study drug (+ 1 day), PTE will occur 7 to 14 days after EOT, and LFU will occur 21 to 28 days after EOT.

The overall study design is as follows (see Table 1):

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 assessments	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 (Section 11).

Subjects must be evaluated directly by the Investigator (i.e., return to clinic for required assessments if being managed in the outpatient setting) from screening/baseline through PTE. If the subject has improved to the point that they have returned to their usual premorbid activity (work/school), and if the primary ABSSSI site has little or no pain, swelling, redness, or purulent/seropurulent drainage at the PTE visit, then the LFU visit, designed to provide an assessment of durability of response, may be performed over the telephone.

In addition, documentation of the primary ABSSSI lesion by digital photography will occur at screening/baseline, EA, Day 7, and EOT. All subjects will have their primary ABSSSI site evaluated by the Investigator, including primary ABSSSI site measurements, as described below.

When conducting a clinical examination of the primary ABSSSI site, the Investigator will perform and record the following:

- Extent of the infection (area in cm^2) as measured by the area of redness, edema, or induration using manual measurement of the longest length multiplied by the greatest perpendicular width, with a ruler provided by the Sponsor. Note that only measurement of the longest length and the greatest perpendicular width (and not calculation of area in cm^2) will be collected and the area in cm^2 will be calculated by the eCRF. Instructions for primary ABSSSI measurements are provided in Appendix 5.
- Local signs and symptoms of erythema (and any distant extension of erythema), swelling/edema, localized warmth, tenderness on palpation, drainage, fluctuance, and induration, as described in Appendix 6.

In addition, record the following information at screening/baseline only:

- Primary anatomical site
- Predisposing cause of infection, if any (e.g., trauma, arthropod bite, fungal dermatosis, surgery, spontaneous, etc.)

Efficacy assessments will include (see Section 9.1 for additional information):

- Early clinical response assessment based on the eCRF data at EA where successful response (i.e., "responder") is defined as a reduction in primary ABSSSI lesion size ≥ 20% compared to baseline, and the subject did not receive a non-protocol specified systemic antibacterial agent with activity against Gram-positive organisms for the treatment of ABSSSI, and did not die of any cause up to EA.
- Investigator's assessment of clinical response at EOT and PTE: Clinical success at EOT and PTE is defined as resolution or near resolution of most baseline ABSSSI signs and symptoms, did not have any surgical procedure to treat the infection after 72 hours post-baseline that was not planned at baseline, no new signs, symptoms, or complications attributable to the ABSSSI, did not receive a 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 or PTE.
- Investigator's assessment of sustained clinical success and clinical relapse/failure at LFU. Sustained clinical success is defined as no new signs or symptoms of primary ABSSSI after PTE. Clinical relapse/failure is defined as new or worsened signs or symptoms of primary ABSSSI after PTE.

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. 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).

Estimated Study Duration:

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.

Number of Subjects:

Up to 200 (133 contezolid acefosamil : 67 linezolid) adult subjects with ABSSSI will be enrolled in this study. Randomization will have a 2:1 (contezolid acefosamil : linezolid) allocation ratio with stratification for ABSSSI type.

Study Drug, Dosage, and Route of Administration:

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.

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.

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 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.

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. The capsules containing contezolid acefosamil tablets and capsules containing linezolid powder will have approximately the same external appearance.

Eligibility Criteria:

Inclusion Criteria:

1. Males or females ≥ 18 years
2. Willing and able to provide written informed consent
3. ABSSSI that is confirmed or suspected to be caused by a Gram-positive pathogen, which meets the following criteria:
   a. Infection of the skin with a lesion size area of at least 75 cm^2, or infection of the central face with a lesion size area of at least 50 cm^2; lesion size measured by the area of redness, edema, or induration using manual measurement of the longest length multiplied by the greatest perpendicular width
   b. One of the following infection types:
      - Cellulitis/erysipelas: A diffuse skin infection characterized by spreading areas of redness, edema, and/or induration
      - Wound infection: An infection characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration, related to trauma or surgery that occurs within 30 days of trauma or surgery
      - Major cutaneous abscess: An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration
4. Clinical findings from both of the following categories within 24 hours:
   a. At least 2 of the following local signs at the ABSSSI site:
      - Purulent or seropurulent drainage/discharge
      - Erythema
      - Fluctuance
      - Heat/localized warmth
      - Pain/tenderness to palpation
      - Swelling/induration
   b. At least 1 of the following signs of systemic inflammation:
      - Fever or hypothermia (PO or rectal temperature ≥ 38.0°C or ≤ 36.0°C)
      - White blood cell (WBC) count ≥ 10,000/mm^3 or ≤ 4,000/mm^3
      - Immature neutrophils (bands) ≥ 10%, irrespective of WBC count
      - Lymphadenopathy or lymphadenitis proximal to the ABSSSI site
      - C-reactive protein (CRP) > upper limit of normal
5. Females must be either postmenopausal for ≥2 years or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) or, if of childbearing potential, must have a negative pregnancy test at screening/baseline and be willing to use a highly effective method of contraception throughout the study such as 1 of the following:
   - Hormonal contraception (stable dose for 3 months)
   - Intrauterine device/intrauterine hormone-releasing system
   - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)
6. Males if sexually active and nonsterile with female partners of childbearing potential must use 2 methods of contraception (i.e., a barrier contraceptive such as condom with spermicidal foam), and be willing to continue to use such highly effective birth control measures while participating in the study and for 70 days following participation in the study. Males must also refrain from sperm donations during this time.

Exclusion Criteria:

1. Prior receipt of any formulation of contezolid acefosamil or contezolid
2. ABSSSI with any of the following characteristics:
   a. Known or suspected to involve anaerobic organisms (e.g., perineal wound infection, gluteal decubitus ulcer, perianal abscess, wound infection associated with surgery on gastrointestinal tract or female genital tract)
   b. Known or suspected invasive infection due primarily to fungal, mycobacterial, parasitic, or viral pathogens
   c. Involving an ischemic ulcer due to peripheral vascular disease
   d. Involving a decubitus ulcer or perirectal abscess
   e. Involving a diabetic foot ulcer
   f. Involving an infected burn
   g. Involving an underlying inflammatory skin disease that may obscure determination of response (e.g., chronic dermatitis) where inflammation may be prominent for an extended period of time, even after successful bacterial eradication has been achieved
   h. Involving pyoderma gangenosum
   i. Involving a bite from a human or animal other than an arthropod
   j. Involving a rapidly necrotizing process, such as necrotizing fasciitis
   k. Involving gangrene of any etiology
   l. Complicated by an immune deficiency in the subject (e.g., development of ecthyma gangrenosum, cellulitis, or wound in a neutropenic subject)
   m. Anatomically associated with prosthetic materials (e.g., venous catheters, permanent cardiac pacemaker battery packs, or joint replacement prostheses), even if the device is removed
   n. An infection complicating an area of the body that will require amputation
   o. Requiring significant surgical intervention (i.e. procedures that would not normally be performed at the bedside) that cannot be performed within 72 hours, unless previously planned, after initiating study drug therapy
   p. Estimated high cure rate after surgical incision alone or after aggressive local skin care (e.g., minor cutaneous abscess or furuncle)
   q. Associated with infection at other anatomic sites or spaces, such as endocarditis or other endovascular infection, thrombophlebitis, osteomyelitis, or septic arthritis
   r. Anticipated need for antibacterial therapy for > 14 days
3. Pre-existing ABSSSI known or suspected to be caused by pathogens that are resistant to oxazolidinone antibiotics
4. Inability to tolerate a PO study drug (e.g., nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of PO study drug)
5. Poor venous access
6. History of any intolerance, hypersensitivity or allergic reaction to any oxazolidinone antibiotic
7. History of any intolerance, hypersensitivity or allergic reaction to aztreonam; note that while cross-reactivity of aztreonam with other β-lactams is rare, this drug should be administered with caution to any subject with a history of hypersensitivity to β-lactams (e.g., penicillins, cephalosporins, and/or carbapenems)
8. History of peripheral or optic neuropathy
9. QTcF interval duration > 450 msec obtained as an average from the triplicate screening/baseline ECGs, history of QT prolongation, hypokalemia (serum potassium < 3.0 mEq/L) at screening/baseline, or other proarrhythmic conditions
10. History of a known or suspected central nervous system (CNS) condition, such as hallucinations, depression, suicidal thoughts or suicidal acts, or of a CNS disorder that may predispose to seizures or lower the seizure threshold

11. History of known or suspected serotonin syndrome, neuroleptic malignant syndrome, or carcinoid syndrome
12. Known or suspected pheochromocytoma or thyrotoxicosis or severe uncontrolled hypertension.
13. History of known or suspected *Clostridium difficile*-associated diarrhea
14. Evidence of significant hepatic, renal, hematologic, or immunologic disease as determined by the following:
    a. Total bilirubin > 2 times upper limit of normal (x ULN)
    b. Alanine amino transferase (ALT) or aspartate amino transferase (AST) > 3 x ULN
    c. Estimated or documented creatinine clearance of < 30 mL/min
    d. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy
    e. Current or anticipated absolute neutrophils< 1500 neutrophils/mm^3
    f. Platelet count < 75,000 cells/mm^3
    g. Infection with human immunodeficiency virus (HIV) and a known CD4 count < 200 cells/mm^3, or another acquired immune deficiency syndrome (AIDS)-defining illness
    h. Receipt of cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs (e.g., cyclosporine, azathioprine, tacrolimus, immune-modulating monoclonal antibody therapy) within the past 3 months, or the receipt of corticosteroids ≥ 10 mg of prednisone (or equivalent) per day for > 14 days in the prior 30 days
15. Females who are pregnant or nursing
16. Prior administration of systemic antibacterial therapy within 96 hours before randomization
    a. 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. 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, or 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)
17. Prior (within the past 2 weeks) administration of, or expected or required concomitant (from the start of the study drug to EOT) administration of:
    a. Systemic adrenergic, dopaminergic, or serotonergic medications
    b. Monoamine oxidase inhibitors (MAOIs) (e.g., isocarboxazid, isoniazid, nialamide, phenelzine, procarbazine, and hydracarbazine)
18. Life expectancy < 3 months or evidence of immediately life-threatening disease, including, but not limited to, current or impending respiratory failure, shock, acute coronary syndrome, unstable arrhythmias, hypertensive emergency, acute hepatic failure, active gastrointestinal bleeding, profound metabolic, or acute cerebrovascular events
19. Unable to cooperate fully with the requirements of the study protocol, including the schedule of assessments, or likely to be non-compliant with any study requirements, or the Investigator determines that the subject should not participate in the study

Pharmacokinetic Assessments:

This study will be conducted at multiple clinical sites, and some will have the appropriate equipment and facilities (including refrigerated centrifuges and -70ºC freezers) and experienced personnel to adequately collect, handle, store, and ship PK samples for bioanalysis. PK assessments will only be performed at selected clinical sites with this capability, and PK samples will be obtained from as many subjects as possible at these selected sites. Drug exposure will be predicted based on demographic data (e.g., body weight) for subjects from whom PK samples were not obtained.

- One PK sample after the 1st IV dose (to characterize the loading dose): obtain 1 blood sample between 0.5 to 2 hours after the end of the 1st infusion
- Three PK samples with the 3rd IV dose (to characterize drug exposure and approaching of steady state):
    - Obtain a 1st blood sample (trough level) within 2 hours before the 3rd IV dose
    - Obtain a 2nd blood sample between 0.5 and 3 hours after the end of the 3rd IV dose
    - Obtain a 3rd blood sample between 4 and 11 hours after the end of the 3rd IV dose but before the 4th dose (IV or PO) of study drug
- Three PK samples at EOT (to evaluate potential drug accumulation):
    - Obtain 1 blood sample (trough level) 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

The PK data acquisition and analysis strategy entail the use of a sparse PK sampling schedule for subjects randomized to contezolid acefosamil. This PK sampling strategy is designed to characterize the impact of the loading dose, and to obtain adequate estimates of drug exposure after the 3rd IV dose and the final IV or PO dose. Additionally, given the range of demographic data in the expected subject population, these PK data will be used to perform exploratory analyses on the impact of demographic characteristics (e.g., weight, body mass index, age, gender, race) upon the PK (including clearance) of the drug and its metabolites. Only those PK samples collected from subjects randomized to contezolid acefosamil will be analyzed. The bioanalytical laboratory will measure plasma concentrations of contezolid acefosamil metabolites (MRX-1352, contezolid, and MRX-1320) using validated and sensitive methods.

Efficacy Endpoints:

The Primary efficacy endpoint is early clinical response at EA for the ITT population as described in Efficacy Assessments above and in Section 9.1.1.

Secondary efficacy endpoints will be determined at EA, Day 7, EOT, PTE, and LFU according to the table below. Early clinical response is defined in Table 2, Investigator's assessment of clinical responses (including success and relapse) are defined in Table 3, per-subject microbiological responses are defined in Section 9.2.2, and microbiological responses per baseline pathogen are defined in Section 9.2.1. The CACO is a composite assessment of the early clinical response at EA and the Investigator's assessment of clinical response at PTE (Section 12.6.2.2).

Efficacy Endpoints	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

Safety and Tolerability Assessments:

Safety will be assessed through the determination and recording of the occurrence of adverse events (AEs) and AEs of special interest, 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.

Statistical Methods:

Sample Size Considerations:

This study is not powered for inferential statistical analysis. Up to 133 subjects (100 evaluable subjects) in the contezolid acefosamil group and up to 67 subjects (50 evaluable subjects) in the linezolid group will allow for planning of future studies. 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.

Analysis Populations:

- ITT Population - All randomized subjects will be included in the ITT population, regardless of whether study drug is administered.
- MITT Population- All randomized subjects in the ITT population, excluding subjects with only Gram-negative pathogen(s) at baseline.
- Safety Population - All subjects who receive any amount of study drug will constitute the safety population. Subjects in the safety population will be analyzed according to study drug received.
- Micro-ITT Population - All randomized subjects in the ITT population who have culture evidence of a baseline Gram-positive bacterial pathogen known to cause ABSSSI.
- CE Populations (CE-EOT, CE-PTE) – All subjects in the ITT population who meet the minimal clinical disease criteria for ABSSSI; receive at least 80% of expected doses based on length of therapy; 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).
  - 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
  - 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 indeterminate unless the subject is deemed a clinical failure at the EOT visit)
    - Had a PTE visit

  In addition to meeting the above criteria, subjects must meet the following specific conditions to be included in the CE populations:
  - Received at least 5 doses of study drug therapy to be considered an evaluable failure
  - Received at least 7 doses of study drug therapy to be considered an evaluable success
  - Did not have any major protocol violation
- ME Population – All subjects in the micro-ITT population who also are in the CE-PTE population.
- PK Population: All subjects who received at least 1 dose of contezolid acefosamil and had at least 1 blood sample collected for analysis of MRX-1352, contezolid, or MRX-1320.

Statistical Analysis:

All baseline data will be summarized by treatment group.

Pharmacokinetic data will be summarized using descriptive statistics and graphically displayed, and population PK modeling analyses will be performed.

The primary efficacy analysis will be based on the early clinical response at EA in the ITT population. The number and percentage of subjects in each treatment group classified as responders will be tabulated and 95% CIs will be provided for each response rate. The 2-sided 95% CI for the difference in response rates between the 2 treatment groups will also be computed. All secondary endpoints will be summarized by treatment group as specified. For outcomes expressed as proportions (other than per-pathogen outcomes), 95% CIs will be presented for descriptive purposes. Additional details will be provided in the Statistical Analysis Plan.

Safety analyses include summaries of treatment-emergent AEs and SAEs, vital signs, laboratory evaluations (hematology, chemistry, and coagulation), and ECG parameters.

Interim Analysis:

An interim analysis is not planned.

Table 1: Schedule of Events

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							
Pregnancy test[21]	X[10]					X		
Estimate CrCl[22]	X							
PK samples[23]		X	X			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
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 (Section 8.1).
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 (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 (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 (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 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 Section 10.3.
22. Calculate estimated CrCl using screening/baseline height (m), actual weight (kg), and serum creatinine (Section 7.1).
23. Obtain PK samples as follows (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 (Section 8.2). 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) (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.

2 INTRODUCTION

2.1 Background

Acute bacterial skin and skin structure infections (ABSSSI) are common infectious diseases; approximately 6.3 million physician's office visits per year are attributable to this infection (Pallin, 2008). The frequency and severity of ABSSSI, and the emergence of resistance to many of the antibacterial agents commonly used to treat this infection, have dramatically increased over the past 2 decades (Stevens, 2014). For example, there was a 29% increase in the total hospital admissions for ABSSSI between 2000 and 2004 (Edelsberg, 2009). In addition, annual emergency department visits for ABSSSI between 1993 and 2005 increased from 1.2 million to 3.4 million patients (Pallin, 2009). Skin and soft tissue infection and ABSSSI in hospitalized patients contribute to prolonged length of stay and increase costs of medical care, as well as play an important role in driving antimicrobial resistance emergence (Rennie, 2003).

The increases in incidence and severity of ABSSSI are in part attributed to the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) (Edelsberg, 2009). Community-associated MRSA has increased markedly to become the greatest problem facing therapy for ABSSSI in the outpatient setting (Deresinski, 2005; Diep, 2004; Eron, 2003). In a large global surveillance study to determine the bacteriology of ABSSSI between 1998 and 2004, *S. aureus* ranked first as the predominant ABSSSI pathogen in all regions studied (North America, Latin America, and Europe); among the North American *S. aureus* isolates, the prevalence of MRSA increased from approximately 42% in 1998 to 52% in 2004 (Moet, 2007).

In the same global surveillance study, the second most frequently isolated Gram-positive pathogen of ABSSSI was *Enterococcus* spp., where the prevalence remained high in North America (approximately 10%) (Moet, 2007). Furthermore, the prevalence of vancomycin-resistant enterococci (VRE) was of greatest concern in North America compared with other regions, where rates of resistance increased from approximately 9% in 1998 to 15% in 2004. In addition to *S. aureus* and enterococci, streptococci (e.g., group A, B, C, or G streptococci) and other staphylococci (e.g., coagulase-negative species) remain important causes of ABSSSI.

It is important to note that ABSSSI may involve aerobic Gram-negative pathogens or may be polymicrobial (Gram-positive, Gram-negative bacteria, and possibly anaerobic bacteria), depending on host factors and risk factors (Stevens, 2014). Therefore, the goal of clinical evaluation of ABSSSI aims to establish the specific microbial cause to help determine optimal pathogen-directed therapy, which takes into account pathogen-specific and local antibiotic resistance patterns. As most cases of ABSSSI are caused by endogenous Gram-positive cocci (i.e., staphylococci and streptococci) —many of which may be drug-resistant—empiric treatment algorithms are no longer simple; recent emerging resistance of *S. aureus* to methicillin, erythromycin, clindamycin, tetracycline, and trimethoprim-sulfamethoxazole—and emerging resistance of streptococci to erythromycin and clindamycin—have dramatically altered options of empiric and definitive therapy.

The oxazolidinone class of antimicrobials have provided an important therapeutic option in the treatment of ABSSSI. Linezolid, the first oxazolidinone, was approved in 2000 and is highly efficacious for the treatment of both community-acquired and hospital acquired infections (Wilcox, 2005). In the US, linezolid is indicated for the treatment of VRE infections (including cases with concurrent bacteremia), nosocomial pneumonia (caused by methicillin-sensitive *S. aureus* [MSSA], MRSA, or *S. pneumoniae*, including multidrug-resistant [MDR] strains), uncomplicated and complicated skin and skin structure infections including diabetic foot infections without concomitant osteomyelitis (caused by MSSA, MRSA, *Streptococcus pyogenes*, or *S. agalactiae*), and community-acquired pneumonia caused by *S. pneumoniae*, including MDR strains and cases with concurrent bacteremia, or MSSA (Zyvox® Prescribing Information, 2018). There is an extremely low propensity toward developing bacterial resistance to linezolid in all target pathogens, even after over 14 years of clinical use. Despite these benefits, linezolid is subject to serious safety limitations, primarily due to myelosuppression and monoamine oxidase inhibition with associated drug-drug interactions, central nervous system (CNS) and blood pressure effects. While myelosuppression is reversible and uncommon with linezolid treatment regimens ≤ 14 days, extended treatment is also associated with mitochondrial toxicity resulting in optical neuropathy with rare but irreversible vision impairments (Zyvox® Prescribing Information, 2018).

In June 2014, tedizolid (Sivextro®), a second oxazolidinone was approved by the Food and Drug Administration (FDA) for the treatment of ABSSSI caused by MSSA, MRSA, various *Streptococcus* species, and *Enterococcus faecalis* (FDA, 2014). The availability of both oral (PO) and intravenous (IV) formulations has added to their clinical utility, as have pharmacokinetic (PK)/pharmacodynamic (PD) characteristics that offer, among other things, a bioavailability of 90 to 100%, possibility of once daily (tedizolid) or twice daily (linezolid) dosing, and excellent and prolonged tissue penetration (Dryden, 2014; Flanagan, 2014).

Introduction of new oxazolidinone compounds that are safe and effective, have a PO and IV formulation, and have important differentiating features over existing agents are needed to ensure continued effective treatment of ABSSSI and other serious Gram-positive infections caused by emerging resistant Gram-positive pathogens.

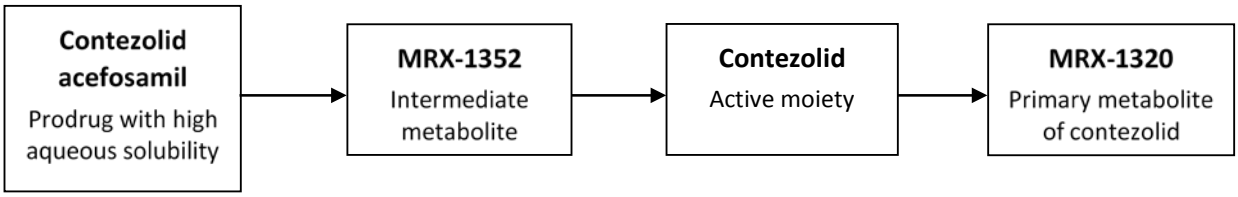
2.2 Description of Contezolid and Contezolid Acefosamil

MicuRx Pharmaceuticals, Inc. pursued a research program to develop a novel oxazolidinone agent that maintains high antibacterial activity while potentially addressing the key toxicity issues associated with linezolid therapy. The initial drug candidate, contezolid (previously referred to as MRX-1), was well tolerated, safe, and shown to have efficacy comparable to linezolid (Gordeev, 2014). Contezolid is a Biopharmaceutics Classification System (BCS) class 2 molecule (poorly soluble in water), and absorption of oral contezolid was markedly improved when administered with food. In addition, the poor solubility made the production of an IV formulation impractical. To address these issues, contezolid acefosamil, a prodrug of contezolid, was developed to decrease the impact of food on oral absorption and to present the patient and physician the opportunity to utilize the same molecular entity for both IV and oral therapy. The main objective of the contezolid acefosamil and contezolid clinical program is to develop oxazolidinone antibiotics with improved tolerability and reduced toxicity compared to

the currently available oxazolidinones (linezolid and tedizolid) while maintaining efficacy in serious Gram-positive bacterial infections.

Contezolid acefosamil, the sodium salt of a contezolid prodrug with high aqueous solubility, degrades into bioactive contezolid in aqueous environments in a 2-step process (Figure 1). In the first step, contezolid acefosamil quickly degrades into an intermediate metabolite, MRX-1352, when given either by the oral (PO) or intravenous (IV) route, and the second step results in the active moiety, contezolid. Additionally, the primary metabolite of contezolid is MRX-1320. The structure of contezolid has been previously published (Gordeev, 2014). Neither contezolid acefosamil nor MRX-1352 have direct antibacterial activity and must be converted to contezolid to become active. Neither contezolid acefosamil, nor MRX-1352, nor the side chain fragments cleaved during biotransformation are associated with unique toxicities in animal models.

Figure 1: Contezolid Acefosamil Metabolites



The complete nonclinical toxicology program with contezolid acefosamil demonstrated the following:

- Whether given PO or IV, contezolid acefosamil has good tolerability and safety, and is comparable to contezolid in preclinical models of efficacy.
- Contezolid acefosamil is well absorbed in animals as a PO agent when dosed with and without food.

A further description of the physical and chemical characteristics of contezolid and contezolid acefosamil is found in the Investigator's Brochure. Contezolid acefosamil is expected to offer similar or more consistent (i.e., improved) PK properties than contezolid and is expected to be available for both IV and PO administration in clinical practice. Therefore, contezolid acefosamil may provide an attractive option for ABSSSI and other significant Gram-positive infections in both hospital and community settings.

2.3 Summary of Relevant Nonclinical Experience

2.3.1 Pharmacology, Microbiology, Toxicology, and Safety

The active pharmaceutical ingredient, contezolid has demonstrated excellent in vitro antibacterial activity against both nosocomial and community Gram-positive pathogens. Oral absorption of contezolid in the mouse, rat, and dog was rapid with maximum time to absorption (T_{max}) of 0.5 to 1 hour and a half-life ($t_{1/2}$) of 1 to 2 hours. The mean effective protective dose (ED_{50}) was similar to linezolid in in vivo mouse models of systemic and local infections caused by MRSA, penicillin-resistant *S. pneumoniae*, and VRE. Moreover, the minimum inhibitory concentration

for 90% of microbial strains (MIC_{90}) is < 2 µg/mL against recent US surveillance isolates (Li, 2014).

After IV administration in rats, contezolid acefosamil was rapidly metabolized into contezolid after 30 minutes; the prodrug, contezolid acefosamil, was not detectable in rat blood specimens (whole blood supernatant specimens). Peak concentrations of contezolid were demonstrated at 0.7 hours. After multiple IV doses of 40 mg/kg contezolid acefosamil in rats, no accumulation of the active molecule or its metabolites were noted over a 7-day period of consecutive administrations. Studies with radiolabeled ^{14}C-MRX-1 indicated primarily fecal excretion within the first 24 hours after PO administration.

In toxicology studies, contezolid was generally well tolerated after 4-week PO dosing in rats and dogs. Results from contezolid acefosamil toxicology studies indicated that contezolid acefosamil was not genotoxic or phototoxic and did not cause sensitization. Contezolid acefosamil did not cause hemolysis or red blood cell coagulation and was generally well tolerated in a vascular irritation study. contezolid acefosamil had negative results on the bacterial reverse mutation test, did not induce any structural or numerical chromosome aberrations in CHO-WBL cells, and showed no evidence of rat bone marrow micronucleus damage or cytotoxicity. The no observed adverse effect level (NOAEL) of contezolid acefosamil for potential reproductive and/or developmental toxicity was 120 mg/kg/dose twice daily (BID) in male and female rats. The NOAEL of contezolid acefosamil for embryo-fetal development retardation was 40 mg/kg/dose BID (80 mg/kg/day: C_{max} = 14,300 ng/mL, area under the curve $[AUC]_{0\text{-}24h}$ = 139,000 h*ng/mL on gestation day 17). Further details regarding the microbiology, and animal PK/PD of contezolid and contezolid acefosamil are available in the contezolid acefosamil IB.

With its improved solubility, contezolid acefosamil is expected to offer similar or more consistent (i.e., improved) PK properties than contezolid, and can be administered by both IV and PO routes of administration in clinical practice. The available in vitro microbiology and in vivo animal efficacy data support continued clinical development of contezolid acefosamil as a potential human therapeutic agent for the treatment of moderate to severe bacterial infections caused by Gram-positive pathogens, most notably MRSA and other drug-resistant Gram-positive pathogens.

2.4 Summary of Relevant Clinical Experience

Contezolid is the active moiety of contezolid acefosamil. Several clinical studies were conducted with contezolid, including 2 Phase 1 clinical studies (MRX-I-01, MRX-I-02) and one proof-of-concept Phase 2 clinical study (MRX-I-03). From the Phase 1 and 2 studies, contezolid administered PO in single or multiple doses up to 800 mg every 12 hours for up to 28 days was well tolerated in healthy adult subjects.

However, the physical and chemical characteristics of the active pharmaceutical ingredient ensured that no commercially practical IV formulation was likely to be developed for contezolid. Thus, research was directed toward finding a related compound with antimicrobial characteristics similar to contezolid but with greater solubility. Contezolid acefosamil, the prodrug of contezolid, fits the required characteristics.

Two clinical studies have been completed with contezolid acefosamil. MRX4-001 was the first-in-human study of PO contezolid acefosamil conducted in healthy volunteers in the US (Section 6.2 of the Investigator's Brochure). MRX4-002 was the first-in-human study of IV contezolid acefosamil in healthy volunteers, and evaluated IV contezolid acefosamil administration and compared both the PO and IV administrations (Section 6.3 of the Investigator's Brochure). An overview of the safety, tolerability, and PK from these studies is presented below, with additional details provided in the Investigator's Brochure.

2.5 Safety and Tolerability of Contezolid Acefosamil

In the Phase 1 contezolid acefosamil studies, safety and tolerability were assessed through adverse event reporting, collection of medical histories and concomitant medications, urine drug screens, urine and serum pregnancy tests, laboratory evaluations including hematology and coagulation tests, urinalyses, physical examinations, vital signs, and electrocardiograms (ECG).

In Study MRX4-001, a total of 122 subjects were exposed to contezolid acefosamil or placebo administered orally in single doses of up to 3000 mg and multiple doses of up to 1500 mg every 12 hours for 10 days. In Study MRX4-002, a total of 98 subjects were enrolled, and 96 subjects were exposed to contezolid acefosamil or placebo administered via IV in single doses of up to 2400 mg and multiple doses of up to 2100 mg QD for 10 days; 12 of 98 subjects also received 2 doses of orally administered contezolid acefosamil 1500 mg q12h in the crossover portion of the study.

In general, in both studies, contezolid acefosamil was well tolerated at these doses, and the safety profile of contezolid acefosamil was consistent with oxazolidinone class effects. Findings included:

- The majority of treatment-emergent adverse events (TEAEs) in both studies were mild in severity.
- There were no severe or serious adverse events (SAEs) or deaths.
- There were no unusual or unexpected TEAEs judged related to study drug.
- Overall, the nature and extent of TEAEs, and treatment-related TEAEs, were similar between all treatment groups for both PO and IV administration, including placebo.
- In Study MRX4-001 (PO administration), discontinuations due to TEAEs were observed in 2 subjects (pyrexia in the 500 mg cohort, judged by the Investigator to be unrelated to study drug and vomiting in the 1500 mg cohort, judged possibly related to study drug). In Study MRX4-002 (IV administration), there were no discontinuations due to TEAEs; however, 1 subject voluntarily withdrew consent from the study due to AEs of nausea, somnolence, asthenia, and headache which occurred within the first 12 hours after receiving a single 1500 mg oral dose and were judged possibly related to study drug.
- During PO administration (Study MRX4-001), the most frequently reported treatment-related TEAEs in study Part 1 (single ascending doses of contezolid acefosamil or placebo) were

headache and nausea. The most frequently reported treatment-related TEAE in Part 2 (multiple ascending doses of contezolid acefosamil or placebo) was nausea. The most frequently reported treatment-related TEAEs during Part 3 (contezolid acefosamil or placebo and omeprazole) were headache, nausea, and vomiting.

- During IV administration (Study MRX-002), the most frequently reported TEAEs for IV contezolid acefosamil and IV placebo involved the infusion site. In Part 1, only 1 AE, dysgeusia, was considered related to IV contezolid acefosamil. In Part 2, the most frequently reported AEs related to IV contezolid acefosamil were infusion site irritation and infusion site pain. In Part 3 (crossover portion investigating IV and oral formulations), the most frequently reported AE related to contezolid acefosamil was headache.

- Two AEs of neutropenia were reported in Study MRX4-001 (all in subjects treated with PO contezolid acefosamil), and 3 in Study MRX4-002 (2 in subjects treated with IV contezolid acefosamil and 1 in subject treated with placebo); all 5 events were National Cancer Institute (NCI) Common Terminology for Adverse Event (CTCAE) Grade 2 (moderate) and none were judged related to study drug.

- No impact of contezolid acefosamil administration (PO or IV) on laboratory values or ECGs interpretations was observed; no clinically significant laboratory values were attributed to the study treatment, and there were no significant results on any ECG interpretation.

- In general, contezolid acefosamil was well tolerated when given orally as a single 1500 mg dose in combination with omeprazole.

For more details on the PK of contezolid acefosamil in the MRX-001 and MRX-002 studies, see Sections 6.2 and 6.3 of the Investigator's Brochure.

2.6 Pharmacokinetics of Contezolid Acefosamil

In Study MRX04-001, the PK of orally administered contezolid acefosamil was evaluated after single ascending doses of 250, 500, 750, 1000, 1500, 2000, 2500, and 3000 mg (including an evaluation of food effect at the 1500 mg dose), multiple ascending doses of 500 mg q12h, 7500 mg q12h, 1000 mg q12h, and 1500 mg q12h for 10 days, and in a crossover study alone at 1500 mg and when co-administered with omeprazole.

In Study MRX4-002, the PK of IV contezolid acefosamil was evaluated after single ascending doses of 150, 300, 600, 1200, 1800, 2100, and 2400 mg, multiple ascending doses of 600 mg q12h, 900 mg q12h, and 2100 mg QD for 10 days, and a crossover study comparing IV (2100 mg) and oral (2 doses of 1500 mg tablets q12h) formulations of contezolid acefosamil.

The general findings are described below.

- Contezolid acefosamil was rapidly metabolized after both single and multiple oral doses of contezolid acefosamil. When contezolid acefosamil was administered orally, no quantifiable contezolid acefosamil concentrations were observed at any of the sampled timepoints, and therefore PK parameters for contezolid acefosamil could not be estimated. When

administered via IV, blood concentrations of contezolid acefosamil increased with dose and declined rapidly after the infusion, with an estimated $T_{1/2}$ of 8 to 11 minutes.

- Contezolid acefosamil concentrations were transient and very low after IV administration and undetectable after oral administration compared with those observed for the contezolid acefosamil metabolites.

- Exposure to the active moiety, contezolid, in blood increased approximately dose-proportionally with increasing oral and IV doses of contezolid acefosamil, particularly after multiple doses. During multiple dosing, there was no apparent accumulation for the 2100 mg QD IV regimen or for oral regimens of up to 1000 mg q12h; however, contezolid concentrations do gradually increase in systemic circulation over time as time to steady state may require up to 7 days when oral or IV contezolid acefosamil is dosed above 1000 mg q12h. Exposure after 10 days may increase up to 2 fold when dosed q12h given IV and up to 1.7 fold when 1500 mg is given orally q12h.

- Exposure to contezolid in blood after orally administered contezolid acefosamil 1500 mg q12h (2 doses separated by 12 hours) was similar to that observed after contezolid acefosamil IV 2100 mg (single dose); the bioavailability of contezolid after orally administered contezolid acefosamil was approximately 66% of that after IV contezolid acefosamil. Based on relative amounts of MRX-1352, contezolid in blood and plasma, and MRX-1320 in plasma, there was no appreciable binding to blood components.

- Although oral administration of contezolid acefosamil 1500 mg under fed conditions resulted in a delay in contezolid T_{max} by approximately 0.8 hours, from 2.42 hours to 3.25 hours, the maximum contezolid exposure (C_{max}) was similar after administration of 1500 mg contezolid acefosamil under fed and fasted conditions; the geometric mean ratio was 91.83%. An increase in total contezolid exposure (AUC_{0-t}, $AUC_{0-\infty}$) of approximately 24% was observed in the presence of food; geometric mean ratios were 123.77% and 123.74%, respectively. Intrasubject variability ranged from 14.78% ($AUC_{0-\infty}$) to 19.20% (C_{max}). Therefore, the drug product can be taken with or without food.

- After co-administration of contezolid acefosamil plus omeprazole, maximum contezolid exposure (C_{max}) was approximately 20% higher compared to that after administration of contezolid acefosamil alone. Total contezolid exposure (AUC_{0-t} and $AUC_{0-\infty}$) was similar across treatments. Intrasubject variability ranged from 16.49% (AUC_{0-t}) to 16.57% ($AUC_{0-\infty}$). Therefore, no significant drug interaction is noted with concomitant omeprazole treatment.

- No clear gender-related trends were observed.

For more details on the PK of contezolid acefosamil in the MRX-001 and MRX-002 studies, see Sections 6.2 and 6.3 of the Investigator's Brochure.

2.7 Summary and Rationale for Study

There is an unmet need for additional antibiotic choices to treat Gram-positive bacterial infections caused by organisms such as MRSA and VRE.

Contezolid acefosamil, a sodium salt of a contezolid prodrug, is a synthetic antibiotic in the oxazolidinone class of antimicrobials. Due to the low solubility of contezolid and inability to produce a practical IV formulation using contezolid, an orally bioavailable and water soluble new molecular entity (contezolid acefosamil) was developed, a full battery of preclinical studies was performed, and a successful Phase 1 program evaluating both the oral and IV formulations of contezolid acefosamil was completed under a US IND.

Contezolid is a novel oxazolidinone with potent in vitro activity against aerobic and anaerobic Gram-positive pathogens, with demonstration of clinical efficacy in ABSSSI in 2 previous Phase 2 studies. Contezolid acefosamil, which rapidly converts to contezolid, is expected to offer patients and physicians an effective and better tolerated option for the treatment of serious Gram-positive bacterial infections. Contezolid acefosamil will be available in both IV and PO formulations.

Both contezolid and contezolid acefosamil have proven to be highly efficacious in various models of animal infections caused by Gram-positive bacteria, including drug-resistant strains of *S. aureus*, *Streptococcus pneumoniae*, and enterococci. The animal models used for evaluation included murine sepsis and thigh infection.

The therapeutic benefit of linezolid (comparator) for the treatment of ABSSSI has been established (Zyvox® Prescribing Information, 2018). Based on linezolid prescribing information, contezolid acefosamil, an oxazolidinone, is contraindicated in patients with known hypersensitivity to oxazolidinones and in patients taking any monoamine oxidase inhibitors (MAOIs) or within 2 weeks of taking an MAOI. Warnings and precautions in the label include the risks for myelosuppression, peripheral and optic neuropathy, serotonin syndrome, *Clostridium difficile*-associated diarrhea, potential drug interactions producing hypertension, and hypoglycemia. Further information is provided in the contezolid acefosamil IB and can also be obtained from the prescribing information for linezolid (Zyvox® Prescribing Information, 2018). Refer to the IB for additional information.

The current study is a Phase 2, multicenter, randomized, double-blind study designed to evaluate the safety and efficacy of IV and PO administered contezolid acefosamil compared to linezolid (Zyvox®) in adult subjects with ABSSSI. The study design incorporates recommendations from the US Food and Drug Administration 2013 Guidance for Industry (ABSSSI: Developing Drugs for Treatment) (FDA, 2013). The primary efficacy endpoint of early clinical response at early assessment aligns with the current FDA guidance. The secondary efficacy endpoint of the Investigator's assessment of clinical response at PTE is based on current EU guidance (EMA, 2013). The safety parameters monitored during the study are well-accepted measures of safety in clinical study subjects. Contezolid acefosamil PK concentrations will not be assessed in this study based on Phase 1 study results indicating rapid conversion (within 0.25 hours) of contezolid acefosamil to MRX-1352, an intermediate metabolite of the prodrug, and subsequent conversion to active contezolid. Blood specimens will be collected to understand the PK performance of contezolid acefosamil tablets used in this study population. The levels of the following contezolid acefosamil metabolites will be assessed: MRX-1352, contezolid, and MRX-1320.

2.8 Rationale for Dose Regimens

The contezolid acefosamil dose regimen chosen for evaluation in this study is derived from 3 lines of evidence:

- From clinical PK/PD studies in the mouse thigh infection model.
- From the Phase 1 studies in which administration of contezolid acefosamil was generally safe and well tolerated when administered to healthy volunteers at doses up to 2100 mg IV QD over 60 minutes for 10 days (MRX4-002), and when contezolid acefosamil was administered at doses up to 1500 mg PO BID for 10 days (MRX4-001).
- Exposure of contezolid in blood after these respective doses was similar, the bioavailability of contezolid after contezolid acefosamil administered PO was approximately 66% of that after contezolid acefosamil administered via IV. And the exposure of 1000 mg of contezolid acefosamil IV q12h and 1300 mg contezolid acefosamil q12h by the PO route only slightly exceed the (contezolid) drug exposure when contezolid is given under optimal conditions.
- From 2 Phase 2 studies which showed that contezolid dosed at 800 mg twice daily was non-inferior to linezolid 600 mg given twice daily.

The linezolid dose regimen is based on the current prescribing information (Zyvox® Prescribing Information, 2018).

3 STUDY DESIGN

3.1 Study Objectives

The objectives of this study are to compare contezolid acefosamil to linezolid in treating ABSSSI that is confirmed or suspected to be caused by Gram-positive pathogens.

Primary:

- 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

Secondary:

- Evaluate early clinical response at:
  - EA in the 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 modified intent-to-treat (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 the 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

3.2 Study Design Details

This is a Phase 2, multicenter, randomized, double-blind safety and efficacy study of contezolid acefosamil 1500 mg 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 (133 contezolid acefosamil : 67 linezolid) will be enrolled to achieve approximately 150 (100 contezolid acefosamil : 50 linezolid) clinically evaluable subjects at approximately 5 to 10 sites within the US and randomized 2:1 (contezolid acefosamil : linezolid) for treatment of ABSSSI that is confirmed or suspected to be due to a Gram-positive bacterial pathogen. Randomization will be stratified by ABSSSI types to better ensure proper balance between the treatment groups. Subjects will receive at least 3 doses of the IV formulation of study drug before switching to the PO formulation. Subjects will receive study drug 10 to 14 days as described in Section 3.5.

Screening/baseline assessments for study eligibility will be performed within 24 hours prior to the start of the first dose of study drug. Subjects who provide informed consent, are willing and able to collaborate and cooperate with study protocol requirements, and meet all study eligibility criteria will be randomized in the study.

Gram stain and culture specimens of the ABSSSI site must 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 cellulitic 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. All ABSSSI site specimens will be processed for Gram stain and culture at the local laboratory, and all blood cultures will be processed at the local laboratory. All bacterial isolates that are identified from an ABSSSI site specimen or blood culture at the local laboratory will be sent to the central laboratory for confirmation of species

identification and antimicrobial susceptibility testing (Section 8.2). Microbiological methods will be detailed in the Laboratory Manual.

If Gram-positive and Gram-negative pathogens are suspected (Gram stain suggests both a Gram-positive and Gram-negative pathogen) or proven from screening/baseline microbiologic laboratory results or history, the subject will be eligible for treatment under this protocol. Subjects with both Gram-positive and Gram-negative pathogens will receive adjunctive antimicrobial therapy with parenteral aztreonam (Section 5.1.3). Subjects with only Gram-negative pathogens are not eligible for continued treatment under this protocol and will be discontinued from the study as soon as Gram stain or culture confirms that the subject's infection has no Gram-positive pathogen contributing to the subject's disease. If no Gram-negative pathogens are isolated from the screening/baseline cultures by Day 3, aztreonam will be discontinued. Subjects with suspected infections primarily due to anaerobic organisms as the cause for ABSSSI or subjects requiring empiric adjunctive anaerobic antimicrobial coverage are excluded from treatment under this protocol.

Prompt enrollment procedures are encouraged to allow for prompt administration of study drug. Subjects who received prior systemic antibacterial therapy with Gram-positive activity within 96 hours prior to randomization are excluded from the study unless clear clinical evidence of prior treatment failure within the prior 96 hours is available (Section 4.2). However, one exception to this criterion is the receipt of a single dose of a short-acting, non-oxazolidinone antibiotic (Section 5.2). Subjects who received a single dose of a short-acting non-oxazolidinone Gram-positive antibiotic within 96 hours prior to randomization will not comprise > 25% of randomized subjects.

It is expected that most subjects will remain in the hospital or clinic while receiving IV treatment with study drug for a minimum of 3 total IV doses; however, subjects who are clinically stable and have adequate home support with reliable transportation to/from the hospital or clinic may leave and return to the hospital or clinic for IV infusions. Study drug IV infusions are not to be administered at home. Subjects may receive the IV formulation for the entire treatment duration. 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, subjects may be switched to the PO formulation. Subjects who are switched from the IV to the PO formulation of study drug must remain in the hospital or clinic for observation for at least 90 minutes after the first PO dose. The subject may be discharged on PO medication only after good tolerability has been demonstrated with the initial dose of PO treatment (Section 3.5).

Subjects will undergo follow-up visits as described in Table 1 and Section 7. Subjects must be evaluated directly by an Investigator (i.e., return to clinic for required assessments if being managed in the outpatient setting) from screening/baseline through PTE. If the subject has improved to the point that they have returned to their usual premorbid activity (work/school), and if the primary ABSSSI site has little or no pain, swelling, redness or purulent/seropurulent drainage at the PTE visit, the LFU visit may be performed over the telephone (Section 8.1). Additionally, documentation of the primary ABSSSI lesion by digital photography will occur at screening/baseline and at various timepoints during and after study treatment (Section 8.3).

ABSSSI specimen Gram stain and cultures will be collected from the primary site of infection at each visit from EA through LFU only if clinically indicated (e.g., the subject is deemed a clinical failure or relapse or purulence and discharge from the ABSSSI site continues after screening/baseline).

Subjects will be monitored for the occurrence of AEs throughout the study, including AEs that are associated with the oxazolidinone class of antibiotics. Physical examinations, vital signs, ECGs, and clinical laboratory tests (hematology, chemistry, coagulation, and UA) will be performed at screening/baseline and at various timepoints during and after study treatment (Table 1).

3.3 Number of Subjects

Up to 200 (133 contezolid acefosamil : 67 linezolid) adult subjects with ABSSSI will be enrolled in this study. Randomization will have a 2:1 (contezolid acefosamil: linezolid) allocation ratio with stratification for ABSSSI type.

3.4 Randomization & Blinding

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. Additionally, subjects who received a single dose of a short-acting non-oxazolidinone Gram-positive antibiotic within 96 hours prior to randomization will not comprise > 25% of randomized subjects.

Subjects will be randomized to treatment provided they meet all inclusion and no exclusion criteria (see Section 4.1 and Section 4.2, respectively). Subjects will be randomized using an interactive web response system (IWRS) to contezolid acefosamil or linezolid with a 2:1 ratio. Randomization will be stratified by ABSSSI type (cellulitis/erysipelas, wound infection, or major cutaneous abscess) to better ensure proper balance between the treatment groups. After informed consent has been obtained and study eligibility established, the study site's Pharmacist or Pharmacist's designee will obtain the study drug assignment from the 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 direct subject care, or those involved in clinical evaluations. 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 Study Procedures Manual.

If study drug is determined not to be safe and/or not tolerated, the study drug assignment for those subjects with a significant safety concern may be unblinded. The Investigator and Medical

Monitor will review the data, discuss the findings, and jointly decide to unblind the treatment assignment, continue enrollment, or terminate enrollment in the study.

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. Emergency unblinding should take place through the IWRS system for both IV and oral doses, and both the Clinical Research Organization (CRO) and the Sponsor should be notified. 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 is 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.

3.5 Study Treatment

Study treatments include contezolid acefosamil and linezolid administered as IV infusions followed by PO dosing as follows:

- Contezolid acefosamil 1500 mg IV will be infused over 60 minutes (± 5 minutes) for 1 dose followed by at least 2 IV doses of 1000 mg IV infused over 60 minutes (± 5 minutes) q12h (± 2 hours) for at least 3 total IV doses, followed by contezolid acefosamil 1300 mg (2 capsules each with 650 mg of contezolid acefosamil) PO q12h (± 2 hours), for a total of 10 to 14 days of treatment.

- Linezolid 600 mg IV will be infused over 60 minutes (± 5 minutes) q12h (± 2 hours) for at least 3 total IV doses, followed by linezolid 600 mg (2 capsules each of 300 mg linezolid) PO q12h (± 2 hours), for a total of 10 to 14 days of treatment.

Treatment with study drug will commence with the IV formulation as soon as possible after eligibility criteria are met. Treatment with the IV formulation will continue for at least 3 total IV doses, after which subjects may be switched to the PO formulation if the primary ABSSSI lesion has not increased in area from the baseline/screening 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; however, subjects may receive the IV formulation for the entire treatment duration. It is expected that most subjects will remain in the hospital or clinic while receiving IV treatment with study drug for a minimum of 3 total IV doses; however, subjects who are clinically stable and have adequate home support with reliable transportation to/from the hospital or clinic may leave and return to the hospital or clinic for IV infusions. Study drug IV infusions are not to be administered at home. Subjects who are switched from the IV to the PO formulation of study drug must remain in the hospital or clinic for observation for at least 90 minutes after the first PO dose, and until the initial dose of the PO formulation is clearly tolerated in the judgment of the Investigator. During outpatient management, subjects will record study drug dosing details on subject-specific drug accountability logs.

To maintain the study blind, both contezolid acefosamil and linezolid PO study drug will be encapsulated to approximate the same external appearance. Either study drug product may be

taken with or without food. Subjects randomized to contezolid acefosamil will receive 2 capsules (650 mg each) q12h (± 2 hours), and subjects randomized to linezolid will receive 2 capsules (300 mg each) q12h (± 2 hours). Additional treatment information is provided in Section 5.

Subjects are to receive 10 to 14 calendar days of study drug. 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).

Prior to any premature discontinuation of study drug, the study site personnel should notify the Medical Monitor if the subject's medical condition allows (see Section 4.6 for follow-up of subjects who prematurely discontinue study drug or study).

3.6 Duration

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 the start of study drug administration on Day 1.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. Males or females ≥ 18 years
2. Willing and able to provide written informed consent
3. ABSSSI that is confirmed or suspected to be caused by a Gram-positive pathogen, which meets the following criteria:
    a. Infection of the skin with a lesion size area of at least 75 cm^2, or infection of the central face with a lesion size area of at least 50 cm^2; lesion size measured by the area of redness, edema, or induration using manual measurement of the longest length multiplied by the greatest perpendicular width
    b. One of the following infection types:
        - Cellulitis/erysipelas: A diffuse skin infection characterized by spreading areas of redness, edema, and/or induration
        - Wound infection: An infection characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration, related to trauma or surgery that occurs within 30 days of trauma or surgery
        - Major cutaneous abscess: An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration
4. Clinical findings from both of the following categories within 24 hours:
    a. At least 2 of the following local signs at the ABSSSI site:
        - Purulent or seropurulent drainage/discharge
        - Erythema
        - Fluctuance
        - Heat/localized warmth
        - Pain/tenderness to palpation
        - Swelling/induration
    b. At least 1 of the following signs of systemic inflammation:

- Fever or hypothermia (PO or rectal temperature ≥ 38.0°C or ≤ 36.0°C)
- White blood cell (WBC) count ≥ 10,000/mm^3 or ≤ 4,000/mm^3
- Immature neutrophils (bands) ≥ 10%, irrespective of WBC count
- Lymphadenopathy or lymphadenitis proximal to the ABSSSI site
- C-reactive protein (CRP) > upper limit of normal

5. Females must be either postmenopausal for ≥2 years or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) or, if of childbearing potential, must have a negative pregnancy test result at screening/baseline and be willing to use a highly effective method of contraception throughout the study such as 1 of the following:
    - Hormonal contraception (stable dose for 3 months)
    - Intrauterine device/intrauterine hormone-releasing system
    - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)
6. Males if sexually active and nonsterile with female partners of childbearing potential must use 2 methods of contraception (i.e., a barrier contraceptive such as condom with spermicidal foam), and be willing to continue to use such highly effective birth control measures while participating in the study and for 70 days following participation in the study. Males must also refrain from sperm donations during this time.

4.2 Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria:

1. Prior receipt of any formulation of contezolid acefosamil or contezolid.
2. ABSSSI with any of the following characteristics:
    a. Known or suspected to involve anaerobic organisms (e.g., perineal wound infection, gluteal decubitus ulcer, perianal abscess, wound infection associated with surgery on gastrointestinal tract or female genital tract)
    b. Known or suspected invasive infection due primarily to fungal, mycobacterial, parasitic, or viral pathogens
    c. Involving an ischemic ulcer due to peripheral vascular disease
    d. Involving a decubitus ulcer or perirectal abscess
    e. Involving a diabetic foot ulcer

f. Involving an infected burn

g. Involving an underlying inflammatory skin disease that may obscure determination of response (e.g., chronic dermatitis) where inflammation may be prominent for an extended period of time, even after successful bacterial eradication has been achieved

h. Involving pyoderma gangenosum

i. Involving a bite from a human or animal other than an arthropod

j. Involving a rapidly necrotizing process, such as necrotizing fasciitis

k. Involving gangrene of any etiology

l. Complicated by an immune deficiency in the subject (e.g., development of ecthyma gangrenosum, cellulitis, or wound in a neutropenic subject)

m. Anatomically associated with prosthetic materials (e.g., venous catheters, permanent cardiac pacemaker battery packs, or joint replacement prostheses), even if the device is removed

n. An infection complicating an area of the body that will require amputation

o. Requiring significant surgical intervention (i.e., procedures that would not normally be performed at the bedside) that cannot be performed within 72 hours, unless previously planned, after initiating study drug therapy.

p. Estimated high cure rate after surgical incision alone or after aggressive local skin care (e.g., minor cutaneous abscess or furuncle)

q. Associated with infection at other anatomic sites or spaces, such as endocarditis or other endovascular infection, thrombophlebitis, osteomyelitis, or septic arthritis

r. Anticipated need for antibacterial therapy for > 14 days

3. Pre-existing ABSSSI known or suspected to be caused by pathogens that are resistant to oxazolidinone antibiotics

4. Inability to tolerate a PO study drug (e.g., nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of PO study drug)

5. Poor venous access

6. History of any intolerance, hypersensitivity or allergic reaction to any oxazolidinone antibiotic

7. History of any intolerance, hypersensitivity or allergic reaction to aztreonam; note that while cross-reactivity of aztreonam with other β-lactams is rare, this drug should be administered

with caution to any subject with a history of hypersensitivity to β-lactams (e.g., penicillins, cephalosporins, and/or carbapenems)

8. History of peripheral or optic neuropathy

9. QTcF interval duration > 450 msec obtained as an average from the triplicate screening/baseline ECGs, history of QT prolongation, hypokalemia (serum potassium < 3.0 mEq/L) at screening/baseline, or other proarrhythmic conditions

10. History of a known or suspected CNS condition, such as hallucinations, depression, suicidal thoughts or suicidal acts, or of a CNS disorder that may predispose to seizures or lower the seizure threshold

11. History of known or suspected serotonin syndrome, neuroleptic malignant syndrome, or carcinoid syndrome

12. Known or suspected pheochromocytoma or thyrotoxicosis or severe uncontrolled hypertension

13. History of known or suspected *Clostridium difficile*-associated diarrhea

14. Evidence of significant hepatic, renal, hematologic, or immunologic disease as determined by the following:

    a. Total bilirubin > 2 times upper limit of normal (x ULN)

    b. Alanine amino transferase (ALT) or aspartate amino transferase (AST) > 3 x ULN

    c. Estimated or documented creatinine clearance (CrCl) of < 30 mL/min

    d. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy

    e. Current or anticipated as absolute neutrophils < 1500 neutrophils/mm^3

    f. Platelet count < 75,000 cells/mm^3

    g. Infection with human immunodeficiency virus (HIV) and a known CD4 count < 200 cells/mm^3, or another acquired immune deficiency syndrome (AIDS)-defining illness

    h. Receipt of cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs (e.g., cyclosporine, azathioprine, tacrolimus, immune-modulating monoclonal antibody therapy) within the past 3 months, or the receipt of corticosteroids ≥ 10 mg of prednisone (or equivalent) per day for > 14 days in the prior 30 days

15. Females who are pregnant or nursing

16. Prior administration of systemic antibacterial therapy within 96 hours before randomization

    a. 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)

17. Prior (within the past 2 weeks) administration of, or expected or required concomitant (from the start of the study drug to EOT) administration of:

    a. Systemic adrenergic, dopaminergic, or serotonergic medications (Appendix 3)

    b. Monoamine oxidase inhibitors (MAOIs) (e.g., isocarboxazid, isoniazid, nialamide, phenelzine, procarbazine, and hydracarbazine)

18. Life expectancy < 3 months or evidence of immediately life-threatening disease, including, but not limited to, current or impending respiratory failure, shock, acute coronary syndrome, unstable arrhythmias, hypertensive emergency, acute hepatic failure, active gastrointestinal bleeding, profound metabolic, or acute cerebrovascular events

19. Unable to cooperate fully with the requirements of the study protocol, including the schedule of assessments, or likely to be non-compliant with any study requirements, or the Investigator determines that the subject should not participate in the study

4.3 Subject Withdrawal from the Study

Subjects should be encouraged to complete all study assessments. All subjects have the right to withdraw at any time during the study without prejudice.

4.4 Replacement of Subjects

None of the subjects will be replaced once they have been randomized.

4.5 Study Termination by Sponsor and Termination Criteria

The Sponsor reserves the right to terminate any investigational site or the clinical study at any time. Reasons for termination may include, but are not limited to, the following:

- Unacceptable safety and tolerability
- The incidence or severity of AEs or SAEs in this study indicates a potential health hazard to subjects
- Serious or persistent noncompliance by the Investigator with the protocol, clinical research agreement, Good Clinical Practice (GCP), or applicable regulatory guidelines in conducting the study
- Institutional Review Board (IRB) decision to terminate or suspend approval for the Investigator
- Investigator request to withdraw from participation
- Subject enrollment is unsatisfactory

4.6 Follow-up of Subjects Prematurely Discontinued from Study Drug or Withdrawn from Study

Subjects who prematurely discontinue study drug will remain in the study. Efforts will be made to complete all protocol-specified assessments listed for the EOT visit at the time of study drug discontinuation (+ 1 day) (Section 7.7), and to perform follow-up safety and outcome assessments specified for the PTE visit (Section 7.8) and the LFU visit (Section 7.9) as scheduled. Complete safety assessments at the EOT visit before beginning rescue therapy, as appropriate. Any ongoing AEs should be followed to resolution or to a satisfactory outcome, as determined by the Investigator.

For subjects who withdraw or are withdrawn from the study itself, efforts will be made to complete all protocol-specified assessments listed for the EOT visit at the time of withdrawal (+ 1 day) (Section 7.7), as appropriate, and to perform follow-up safety assessments as specified for the PTE visit (Section 7.8) and the LFU visit (Section 7.9) as scheduled. Complete the safety assessments at the EOT visit before beginning rescue therapy, as appropriate. Any ongoing AEs should be followed to resolution or to a satisfactory outcome, as determined by the Investigator. Subjects who withdraw will not be replaced.

5 TREATMENT OF SUBJECTS

5.1 Study Drug

5.1.1 Contezolid Acefosamil Study Drug

Contezolid acefosamil study drug will be supplied as lyophilized powder for reconstitution as an IV formulation and an immediate release oral formulation. The clinical label will identify the product by name, lot number, Sponsor, storage conditions, and expiry date. Administration of the study drug is limited for investigational use only. Refer to the Pharmacy Manual for additional information.

5.1.1.1 Contezolid Acefosamil for Intravenous Administration

Contezolid acefosamil drug product will be supplied in 20 ml vials containing 1000 mg, of contezolid acefosamil, 24.53 mg of sodium citrate dihydrate, and 9.60 mg of citrate is produced by filter sterilization and lyophilization. The drug product was produced for the Sponsor by Lyophilization Services of New England.

The drug product powder is to be reconstituted in 300 mL of 5% dextrose in water (D5W) or normal saline (NS) for intravenous administration. The first IV dose of contezolid acefosamil will be 1500 mg, and all subsequent IV doses will be 1000 mg each. The contezolid acefosamil solution in either a diethylhexyl phthalate (DEHP) containing or non-DEHP containing IV bag is stable for up to 16 hours at 25ºC (77ºF), and stable for up to 48 hours at 4ºC (39.2ºF). To ensure long term stability of the drug product, the lyophilized vials will be maintained at -20ºC at the investigative site until it is to be reconstituted for use in the clinic.

An unblinded pharmacist will prepare and blind the contezolid acefosamil IV infusion and will be unblinded to the subject's assigned treatment; however, all other staff will be blinded to the subject's treatment. Please refer to the Pharmacy Manual for details on dose preparation and administration.

5.1.1.2 Contezolid Acefosamil for Oral Administration

Contezolid acefosamil for PO administration is an immediate-release tablet containing 650 mg contezolid acefosamil. To maintain the study blind, contezolid acefosamil tablets will be over-encapsulated to approximate the same external appearance as linezolid study drug. All PO doses of contezolid acefosamil will be 1300 mg (2 capsules). Contezolid acefosamil capsules will be included as part of a blinded kit to ensure all study staff will be blinded to the subject's treatment.

5.1.2 Linezolid Study Drug

Linezolid (Zyvox®) is an FDA-approved commercially available product and will be supplied as IV and PO formulations. The clinical label will identify the product by name, lot number, Sponsor, storage conditions, and expiry date. Refer to the Pharmacy Manual for additional information.

5.1.2.1 Linezolid for Intravenous Administration

Linezolid for IV administration will be provided as 300 mL (600 mg linezolid) single-use, ready to use flexible plastic infusion bags in a foil laminate overwrap. All IV doses of linezolid will be 600 mg. Please refer to the Pharmacy Manual for details on dose preparation and administration. The unblinded pharmacist will prepare and blind the linezolid IV infusion and will be unblinded to the subject's assigned treatment; however, all other staff will be blinded to the subject's treatment.

5.1.2.2 Linezolid for Oral Administration

Linezolid for PO administration will be provided as 300 mg capsules. To maintain the study blind, linezolid capsules will approximate the same external appearance as contezolid acefosamil study drug. All PO doses of linezolid will be 600 mg (2 capsules). Capsules containing linezolid will be included as part of a blinded kit to ensure all study staff will be blinded to the subject's treatment.

5.1.3 Adjunctive Therapy

Linezolid has no useful antimicrobial activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections; it is critical that specific Gram-negative therapy with aztreonam be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected. The PK of linezolid and aztreonam are not altered when co-administered (Zyvox® Prescribing Information, 2018).

According to standard of care treatment guidelines, subjects will receive adjunctive antimicrobial therapy with parenteral aztreonam (1 to 2 g IV/ intramuscular (IM) q8h, not to exceed 6 g/day) for confirmed or suspected aerobic Gram-negative pathogens as causes of the ABSSSI in addition to Gram-positive pathogens. Outpatients may receive either IM or IV aztreonam at the Investigator's discretion (e.g., IV aztreonam may be administered as outpatient parenteral antibiotic therapy in an infusion center). If no Gram-negative pathogen is isolated from the screening/baseline cultures by Day 3, aztreonam is to be discontinued.

Parenteral aztreonam will be provided by the study sites and should be prepared and administered in accordance with current FDA label information (Azactam® Package Insert, 2013).

5.1.4 Dose Adjustment

No adjustments to study drug doses or frequencies are allowed.

5.1.5 Study Drug Compliance

Each dose of IV study drug will be administered by study staff, who are oriented to the details of the clinical protocol and under direct supervision by the Investigator.

The following study drug compliance information will be documented as study information and reported in the electronic case report form (eCRF):

- The dates and times of administration of each IV study drug infusion.

- For IV infusion, the infusion start and stop times will be recorded, and specify if the total volume of study drug solution was administered (if infusion is halted or interrupted for any reason, record the time of premature discontinuation and re-initiation of infusion). An unblinded member of the study staff will inspect the infusion line and bag at the end of infusion to confirm that the full dose has been infused, followed by a rapid IV push to clear any residual study drug in the line. Infusion bags will be retained by the pharmacy for drug accountability purposes until after the study close-out monitoring visit by the unblinded monitor.

- The total volume infused for IV infusion, and number of capsules administered for PO administration.

For any infusion that is incomplete or otherwise not administered over 60 minutes (± 5 minutes), the actual volume infused, infusion duration, and conditions or complications that prevented complete and/or timely administration must be documented. In any case, study site personnel should strive to administer the entire dose regardless of the inter-current problems of drug administration.

Recording of the date and whether each dose of study drug was administered will be used to document compliance with the assigned dosing regimen for oral drug. Subjects managed as outpatients will be given diaries to log times and dates of study drug administration; this information will be entered in the eCRF. The determination of blood concentrations of contezolid acefosamil (and metabolites) during the analytical phase will serve as a further check of compliance.

5.1.6 Study Drug Storage

Unused study drug supplies should be stored according to the directions on the study drug labels.

- Contezolid acefosamil: Lyophilized contezolid acefosamil (for IV formulation) must be stored in a secure area (e.g., a locked freezer), protected from moisture, and kept at or below -20°C until the time of preparation for study drug administration. Once reconstituted with D5W or NS, the solution is stable in either a DEHP containing or non-DEHP containing IV bag for up to 16 hours at 25ºC (77ºF), and stable for up to 48 hours at 4ºC (39.2ºF). Contezolid acefosamil capsules (over-encapsulated tablets) must be stored at 2 to 8ºC (35.6 to 46.4ºF) at the study site but can be stored at 20 to 25ºC (68 to 77ºF) after dispensing to the study subject for up to 7 days.

- Linezolid: Store infusion bags at 20 to 25ºC (68 to 77ºF) and protect from light. It is recommended that the infusion bags be kept in the overwrap until ready to use. Each overwrap contains a peel-off label. Apply the peel-off label to the infusion bag for barcode scanning before use. Protect infusion bags from freezing (Zyvox® Prescribing Information,

2018). For linezolid capsules, please refer to storage instructions for contezolid acefosamil capsules. Keep bottles tightly closed to protect from moisture.

Refer to the Pharmacy Manual for any additional storage, handling, or updated stability data of the study drug supplies.

5.1.7 Study Drug Accountability

All supplies of contezolid acefosamil and linezolid required for completion of this study will be provided by the Sponsor. Adjunctive therapy with aztreonam will be supplied by the study sites.

The unblinded pharmacy personnel are responsible for ensuring that a current record of inventory and drug accountability is maintained during study conduct. A specifically designated unblinded study monitor or designee will be responsible for drug accountability at the site. The Investigator is ultimately responsible for ensuring that a current record of inventory/drug accountability is maintained. Inventory and accountability records must be readily available for inspection by the Sponsor or designee, or applicable regulatory authorities at any time.

Each shipment of study drug will contain a packing slip or equivalent to assist in maintaining current and accurate inventory records. Upon receipt of the study drug, the unblinded pharmacy personnel will visually inspect the shipment and verify the number and condition of study drug (vials, infusion bags, capsules) received. Refer to the Pharmacy Manual for additional information.

Sites will be provided with subject-specific drug accountability logs and subjects will be instructed to maintain a diary of their drug dosing during outpatient management throughout the treatment period.

5.1.8 Study Drug Handling and Disposal

Only upon written authorization from MicuRx or its representative, all partially used study drug must be destroyed at the investigative site or at another site designated by the Sponsor. Unopened drug kits will be destroyed at a site designated by the Sponsor. The Investigator is responsible for ensuring that MicuRx, or its representative, has provided written authorization that procedures for proper disposal of the study drug have been established, and that appropriate records of the disposal are documented and maintained.

5.2 Prior & Concomitant Therapy

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. Only concomitant antimicrobial agents and concomitant medications taken for an AE between EOT and LFU will be documented. Any changes in prior or concomitant medications will also be recorded.

Subjects who have received prior systemic antibacterial therapy within 96 hours prior to randomization are generally excluded from the study; however, exceptions to this criterion include:

- Receipt of a short-acting, systemic, non-oxazolidinone antibiotic and
- Clear failure of an alternative course of prior antibiotic therapy (Section 4.2, Appendix 1).

In addition, the following medications are not allowed from 2 weeks prior to administration of study drug through EOT (Section 4.2):

- Systemic adrenergic, dopaminergic, or serotonergic medications (Appendix 3)
- Any MAOI (e.g., isocarboxazid, isoniazid, nialamide, phenelzine, procarbazine, and hydracarbazine)

Concomitant topical or systemic antibacterial therapy, other than study drug and adjunctive parenteral aztreonam, is not allowed between screening/baseline and PTE (unless the subject is a clinical failure).

The following additional adjunctive therapy is allowed, as clinically indicated:

- Daily dressing changes
- Topical solutions including nonspecific antimicrobial solutions (e.g., povidone-iodine); however, topical therapy with specific antibacterial activity is not allowed (e.g., mupirocin, retapamulin, fusidic acid)
- Surgical debridement
- Hyperbaric oxygen treatments
- Surgical interventions (i.e., incision and drainage, aspiration puncture, or excision with or without grafting) planned at the initiation of treatment through 72 hours after the start of dosing

6 SUBJECT RESTRICTIONS

Subjects are required to:

- Avoid taking any of the following concomitant medications between Day 1 (first administration of study drug) and EOT (last calendar day of study drug).
    - Any adrenergic, dopaminergic, or serotonergic medication, including selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (Appendix 3).
    - Any MAOI (e.g., isocarboxazid, isoniazid, nialamide, phenelzine, procarbazine, and hydracarbazine).
    - Any non-study systemic antibiotic or topical antimicrobial therapy with specific antibacterial activity (e.g., topical mupirocin, retapamulin, or fusidic acid); note that the use of topical solutions including nonspecific antimicrobial solutions (e.g., povidone-iodine) are allowed.
    - *Note*: While hypoglycemic medications are not contraindicated, such agents (e.g., insulin or PO hypoglycemic) should be used with caution. Postmarketing cases of-symptomatic hypoglycemia have been reported in subjects with diabetes mellitus receiving hypoglycemic agents when treated with linezolid. While a causal relationship between linezolid (or other oxazolidinones) and hypoglycemia has not been established, diabetic subjects should be cautioned of potential hypoglycemic reactions when treated with study drug. If hypoglycemia occurs, a decrease in the dose the hypoglycemic agent, or discontinuation of the hypoglycemic agent and/or study drug may be required.
- Avoid consumption of large amounts of foods or beverages with high-tyramine content, including those foods that have been processed by aging, fermentation, pickling, or smoking to improve flavor (e.g., aged cheeses, fermented or air-dried meats, sauerkraut, soy sauce, tap beers) from Day 1 to EOT; see Appendix 2 for a detailed list.
- Females must be either postmenopausal for ≥2 years or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) or, if of childbearing potential, must have a negative serum or urine pregnancy test (β-HCG) at screening/baseline and be willing to use a highly effective method of contraception throughout the study such as 1 of the following:
    - Hormonal contraception (stable dose for 3 months)
    - Intrauterine device/intrauterine hormone-releasing system
    - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)
- Males (if sexually active and nonsterile) with female partners of childbearing potential must use 2 methods of contraception (i.e., a barrier contraceptive such as condom with spermicidal foam) and be willing to continue to use these same birth control measures while participating

in the study (and for 70 days following participation in the study). Males must also refrain from sperm donations during this time.

7 STUDY PROCEDURES

The schedule of events is provided in Table 1.

- Written informed consent must be obtained prior to initiating any study assessment or procedure.

- It is expected that most subjects will remain in the hospital or clinic while receiving IV study drug for a minimum 3 infusions; however, subjects who are clinically stable and have adequate home support with reliable transportation to/from the hospital or clinic may leave and return to the hospital or clinic for IV infusions. Study drug IV infusions are not to be administered at home. Subjects who are switched to the PO formulation of study drug must remain in the hospital or clinic for observation for at least 90 minutes after the first PO dose, and until the initial dose(s) of the PO formulation are clearly tolerated in the judgment of the Investigator (Section 3.5).

- All assessments and procedures on dosing days are obtained predose, unless otherwise specified.

- After screening/baseline, microbiological assessments (ABSSSI site and/or blood cultures) should be repeated only if clinically indicated (e.g., if a subject is deemed a clinical failure or if purulence and discharge from the ABSSSI site continues after screening/baseline).

- Refer to Section 4.6 for follow-up of subjects who prematurely discontinue study drug or the study.

7.1 Screening/Baseline

Study eligibility must be confirmed within 24 hours prior to the first administration of study drug. The following screening/baseline assessments and procedures will be performed ≤24 hours of first dose (see Table 1 for those assessments that need to be repeated predose on Day 1 if the first dose of study drug is administered > 24 hours after the screening/baseline assessments):

- Obtain written informed consent prior to initiating any study-related assessment or procedure

- Obtain complete medical and surgical history

- Obtain prior and concomitant medication history. Record all prior medications taken within 2 weeks prior to randomization (Section 5.2).

- Perform ABSSSI clinical assessments:

    - Perform primary ABSSSI site measurement and a direct evaluation of signs and symptoms of ABSSSI (Section 8.1, Appendix 5, Appendix 6).

    - Perform digital photography of the primary ABSSSI lesion with a digital camera provided by the Sponsor (Section 8.3, Appendix 7).

- 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).

- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature). 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.

- Record height and weight.

- Obtain triplicate 12-lead ECG recordings within a 15-minute period, each separated by at least one minute. The ECG recordings will be obtained prior to collection of blood laboratory samples. All ECGs will be performed using the ECG machines provided by eResearch Technologies (eRT) and will be sent to eRT for central reading.

- Assess, identify, and record any AEs or SAEs from the time the informed consent is signed.

- Perform microbiological assessments (see Section 8.2); additional microbiological specimen collection and processing details are available in the Laboratory Manual:

    - Obtain appropriate ABSSSI site specimen for bacterial culture and Gram stain from all subjects and refer the specimens for Gram stain and culture to the local laboratory for processing. The ABSSSI site specimen should be obtained before administration of antibacterial therapy whenever possible. Repeat ABSSSI specimen cultures and Gram stain at subsequent visits only if clinically indicated (e.g., if subject is deemed a clinical failure or purulence and discharge at the ABSSSI site continues after screening/baseline).

    - Obtain 2 sets of blood cultures (each consisting of 1 aerobic and 1 anaerobic blood culture bottle from 2 separate venipuncture sites) from all subjects. 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. If the repeat blood culture remains positive with the bacterial pathogen initially isolated, the Investigator must consider modifying the subject's antibiotic therapy and discuss the case with the Medical Monitor.

- Record if the subject's premorbid activities (work/school) are compromised

- Obtain samples for laboratory assessments (see Appendix 4 for specific tests). Laboratory samples for screening/baseline will be drawn and sent to both the local laboratory (for eligibility) and to the central laboratory.

    - Obtain blood samples for hematology, chemistry, CRP, serology, and coagulation tests.

- Obtain urine sample for UA (includes urine microscopy if UA is positive for RBCs, WBCs, or protein).
- Perform serum or urine β-HCG pregnancy test for females of childbearing potential up to 2 years postmenopause. (Alternatively, females must be surgically sterile, i.e., have had a tubal ligation, hysterectomy, or bilateral oophorectomy.)
- Obtain the subject's estimated CrCl. The subject's estimated CrCl will be calculated by the local laboratory (for eligibility purposes) using screening/baseline height (m), actual weight (kg), and serum creatinine:

Males:

$$\text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

- Verify that the subject meets all inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2).

7.2 Day 1

Day 1 is the first day of study drug administration; subsequent study days are consecutive calendar days. Select screening/baseline assessments need to be repeated on Day 1 (predose) if the screening/baseline assessments occurred > 24 hours before the first dose of study drug is administered (see Table 1). Eligible subjects are randomized on Day 1. It is expected that most subjects will remain in the hospital or clinic while receiving the IV formulation of study drug for a minimum of 3 IV doses; however, subjects who are clinically stable and have adequate home support may leave and return to the hospital or clinic for IV infusions. Study drug IV infusions are not to be administered at home (Section 3.5).

The following will be performed on Day 1:

- Verify the subject meets all inclusion criteria and exclusion criteria before randomization (Section 4.1 and Section 4.2, respectively).
- Randomize the subject to treatment.
- IV study drug will be administered q12h (± 2 hour) as described in Section 3.5.
- A PK sample will be collected from those who elect to participate in the PK portion of the study between 0.5 and 2 hours after the 1st IV dose, as outlined in Section 11.

- Obtain triplicate 12-lead ECG recordings within a 15-minute period, each separated by at least one minute, within 1 hour prior to the start of IV infusion and 2 hours after the completion of the IV infusion. The ECG recordings will be obtained prior to collection of any blood laboratory samples.

- Assess, identify, and record any AEs or SAEs.

Refer to Section 4.6 for follow-up of subjects who prematurely discontinue study drug or the study.

7.3 Day 2

On Day 2, subjects continue to receive the IV formulation of study drug to complete at least a total of 3 infusions. Subjects who are switched from the IV to the PO formulation of study drug must remain in the hospital or clinic for observation for at least 90 minutes after the first PO dose, and until the initial dose of the PO formulation is clearly tolerated in the judgment of the Investigator (Section 3.5).

No specific assessments or procedures are scheduled on Day 2 except PK samples at select sites:

- Obtain specimen for PK assessments at specified sites for selected subjects:

    - Obtain a 1st blood sample (trough level) within 2 hours before the 3rd IV dose, 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 the 3rd IV dose but before the 4th dose of study drug (IV or PO).

In-person evaluation by the Investigator is not required unless clinically indicated (e.g., perform microbiological assessments, including ABSSSI site specimen and blood cultures, only if clinically indicated [e.g., if study drug is prematurely withdrawn for insufficient therapeutic effect]). Subjects continue to receive blinded study drug q12h (± 2 hours) and any new concomitant medications and AEs or SAEs are recorded.

Refer to Section 4.6 for follow-up of subjects who prematurely discontinue study drug or the study.

7.4 Early Assessment

Perform EA assessments 48 to 72 hours after the start of the first dose of IV study drug. Clinical assessments of ABSSSI from this visit will be used to programmatically determine the clinical response based on data recorded on the eCRF (Section 9.1.1). If the subject is receiving adjunctive antimicrobial therapy with aztreonam and no Gram-negative pathogen is isolated from the screening/baseline cultures by Day 3, aztreonam should be discontinued (Section 5.1.3).

The following will be performed:

- Record any new concomitant medications; verify the subject is not taking any restricted medications (Section 6).
- Perform ABSSSI clinical assessments:
    - Perform primary ABSSSI site measurement and a direct evaluation of signs and symptoms of ABSSSI (Section 8.1, Appendix 5, Appendix 6).
    - Perform digital photography of the primary ABSSSI lesion with a digital camera provided by the Sponsor (Section 8.3, Appendix 7).
- Perform a limited, symptom directed physical examination as clinically indicated.
- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature) as described in Section 7.1.
- Obtain triplicate 12-lead ECG recordings within a 15-minute period, each separated by at least one minute, prior to collection of laboratory (including PK) blood samples. Time of prior dose of study drug and relationship of time of ECG to dose must be documented.
- Assess, identify, and record any AEs or SAEs.
- Perform microbiological assessments as described in Section 7.1 and Section 8.2, including ABSSSI site specimen (if clinically indicated) and blood cultures (if previous blood culture was positive or if clinically indicated).
- Obtain samples for laboratory assessments after a minimum 8-hour fast (Appendix 4):
    - Obtain blood samples for hematology, chemistry, CRP, and coagulation tests.
    - Obtain urine sample for UA (includes urine microscopy if UA is positive for RBCs, WBCs, or protein).
- Continue study drug administration q12h (± 2 hours). If the subject received optional adjunctive parenteral aztreonam and no Gram-negative pathogen was isolated from ABSSSI site specimen culture or blood culture by Day 3, aztreonam must be discontinued (Section 5.1.3).

Refer to Section 4.6 for follow-up of subjects who prematurely discontinue study drug or the study.

7.5 Early Assessment to Day 6

No specific assessments or procedures are scheduled between EA and Day 6. In-person evaluation by the Investigator need not occur unless clinically indicated. Examples include:

- Clinically indicated microbiological assessments as described in Section 7.1 and Section 8.2, including ABSSSI site specimen (if clinically indicated) and blood cultures (if previous blood culture was positive or if clinically indicated).

- Investigator has determined that the subject may be switched from the IV formulation of study drug to the PO formulation.

Record any new concomitant medications and record any AEs or SAEs if the subject is seen during an unscheduled visit.

Refer to Section 4.6 for follow-up of subjects who prematurely discontinue study drug or the study.

7.6 Day 7

The subject will be seen on Day 7 (± 1 day) primarily for safety assessments and to evaluate for signs and symptoms of ABSSSI. The following will be performed:

- Record any new concomitant medications; verify the subject is not taking any restricted medications (Section 6).

- Perform ABSSSI clinical assessments:

    - Perform primary ABSSSI site measurement and a direct evaluation of signs and symptoms of ABSSSI (Section 8.1, Appendix 5, Appendix 6).

    - Perform digital photography of the primary ABSSSI lesion with a digital camera provided by the Sponsor (Section 8.3, Appendix 7).

- Perform a limited, symptom directed physical examination as clinically indicated.

- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature) as described in Section 7.1.

- Assess, identify, and record any AEs or SAEs.

- Perform microbiological assessments as described in Section 7.1 and Section 8.2, including ABSSSI site specimen (if clinically indicated) and blood cultures (if previous blood culture was positive or if clinically indicated).

- Obtain samples for laboratory assessments after a minimum 8-hour fast (Appendix 4):

    - Obtain blood samples for hematology, chemistry, CRP, and coagulation tests.

    - Obtain urine sample for UA (includes urine microscopy if UA is positive for RBCs, WBCs, or protein).

- Continue study drug administration q12h (± 2 hours)

Refer to Section 4.6 for follow-up of subjects who prematurely discontinue study drug or the study.

7.7 End of Therapy

Perform EOT assessments on the last calendar day of study drug administration (or the next day). The EOT visit will alternatively be performed for subjects who withdraw from study drug treatment (Section 4.6).

Subjects will receive study drug for 10 to 14 days as described in Section 3.5. If a subject requires a longer course of therapy for any reason (e.g., unresolved ABSSSI, *S. aureus* bacteremia, deep-seated abscesses [e.g., psoas abscess, epidural abscess], osteomyelitis, endocarditis), the subject will be deemed a clinical failure and open-label antimicrobial(s) should be started, at the discretion of the Investigator. Such cases must be discussed with the Medical Monitor.

The following will be performed:

- Record any new concomitant medications; verify the subject is not taking any restricted medications (Section 6).
- Perform ABSSSI clinical assessments:
    - Perform ABSSSI site measurement and a direct evaluation of signs and symptoms of ABSSSI (Section 8.1, Appendix 5, Appendix 6).
    - Perform digital photography of the primary ABSSSI lesion with a digital camera provided by the Sponsor (Section 8.3, Appendix 7).
    - Perform Investigator's assessment of clinical response (Section 9.1.2).
- Perform a complete physical examination, including eye examination [i.e., Snellen visual acuity and visual field testing] as described in Section 7.1.
- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature) as described in Section 7.1.
- Obtain triplicate 12-lead ECG recordings within a 15-minute period, each separated by at least one minute. The ECG recordings will be obtained prior to collection of blood laboratory (including PK) samples. Time of prior dose of study drug and relationship of time of ECG to dose must be documented.
- Assess, identify, and record any AEs or SAEs.

- Record the date the subject returned to premorbid level of activity (work/school), as applicable.

- Perform microbiological assessments as described in Section 7.1 and Section 8.2, including ABSSSI site specimen (if clinically indicated) and blood cultures (if previous blood culture was positive or clinically indicated).

- Obtain samples for laboratory assessments after a minimum 8-hour fast (Appendix 4):

    - Obtain blood samples for hematology, chemistry, CRP, and coagulation tests.

    - Obtain urine sample for UA (includes urine microscopy if UA is positive for RBCs, WBCs, or protein).

    - Obtain blood or urine sample for β-HCG pregnancy test (females of childbearing potential up to 2 years postmenopause). (Alternatively, females must be surgically sterile; i.e., have had a tubal ligation, hysterectomy, or bilateral oophorectomy.)

- Obtain specimen for PK assessments at specified sites for selected subjects:

    - Obtain one blood sample (trough level) 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 (Section 11).

Refer to Section 4.6 for follow-up of subjects who prematurely discontinue study drug or the study.

7.8 Post Therapy Evaluation

Perform PTE assessments 7 to 14 days after EOT. The following will be performed:

- Record any new concomitant medications (antimicrobial agents only).

- Perform clinical assessments:

    - Perform a direct evaluation of signs and symptoms of ABSSSI (Section 8.1, Appendix 5, Appendix 6).

    - Perform Investigator's assessment of clinical response (Section 9.1.2).

- Perform a limited, symptom directed physical examination as clinically indicated.

- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature) as described in Section 7.1.

- Obtain triplicate 12-lead ECG recordings within a 15-minute period, each separated by at least one minute. The ECG recordings will be obtained prior to collection of blood laboratory samples.
- Assess, identify, and record any AEs or SAEs.
- Record the date the subject returned to premorbid level of activity (work/school), as applicable.
- Perform microbiological assessments as described in Section 7.1 and Section 8.2 including ABSSSI site specimen (if clinically indicated) and blood cultures (if previous blood culture was positive, or if clinically indicated).
- Obtain samples for laboratory assessments after a minimum 8-hour fast (Appendix 4):
    - Obtain blood samples for hematology, chemistry, CRP, and coagulation tests.
    - Obtain urine sample for UA (urine microscopy if UA is positive for RBCs, WBCs, or protein).

Refer to Section 4.6 for follow-up of subjects who prematurely discontinue from the study.

7.9 Late Follow-up

The LFU assessment, designed to provide an assessment of durability of response, is performed 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 ABSSSI site had little or no pain, swelling, redness, or purulent/seropurulent drainage at the PTE visit, then the LFU visit may be performed over the telephone. Symptoms related to possible relapse of ABSSSI (primary site) will be evaluated as part of the safety assessment. If conducted by telephone and clinical relapse/failure is suspected, the subject should be examined and evaluated in-person.

The following will be performed:

- Record any new concomitant medications (antimicrobial agents only).
- Perform Investigator's assessment of clinical response (Section 9.1.2).
- Record the date the subject returned to premorbid level of activity (work/school), as applicable.
- Assess, identify, and record any AEs or SAEs.

8 ASSESSMENT OF THE ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTION

8.1 Clinical Assessments

All subjects must have their primary ABSSSI site evaluated by the Investigator, including ABSSSI site measurements described below. Digital photographs of the ABSSSI site will also be taken as described in Section 8.3. When conducting a clinical examination of the primary ABSSSI site, the Investigator will perform and record the following:

- Extent of the infection (area in cm^2), as measured by the area of redness, edema, or induration using manual measurement of the longest length multiplied by the greatest perpendicular width, with a ruler provided by the Sponsor. Note that only measurement of the longest length and the greatest perpendicular width (and not calculation of area in cm^2) will be collected and the area in cm^2 will be calculated by the eCRF. Instructions for primary ABSSSI measurements are provided in Appendix 5.

- Local signs and symptoms of erythema (and any distant extension of erythema), swelling/edema, localized warmth, tenderness on palpation, drainage, fluctuance, and induration as described in Appendix 6.

In addition, record the following information at screening/baseline only:

- Primary anatomical site

- Predisposing cause of infection, if any (e.g., trauma, arthropod bite, fungal dermatosis, surgery, spontaneous, etc.)

8.2 Microbiological Assessments

As detailed in Section 7.1, all subjects enrolled with ABSSSI in this study must undergo microbiological assessments (i.e., ABSSSI site specimens and blood cultures) at screening/baseline and these samples should be obtained from all subjects prior to administration of antibacterial therapy whenever possible.

The screening/baseline microbiological assessments are critical, in that microbiological response is an important secondary outcome of the study (Section 3.1). Also, the antibacterial spectrum of study drug (contezolid acefosamil or linezolid) is limited to Gram-positive pathogens (e.g., staphylococci and streptococci); therefore, it is important to determine whether non-Gram-positive pathogens are involved in the ABSSSI, in addition to Gram-positive pathogens. Adjunctive parenteral aztreonam should be administered for confirmed or suspected aztreonam-susceptible aerobic Gram-negative pathogens as causes of the ABSSSI in addition to Gram-positive pathogens (Section 5.1.3); however, subjects with suspected Gram-negative pathogens only (e.g., infection caused by *Pseudomonas aeruginosa* in a subject with severe burns) must be excluded. Similarly, polymicrobial ABSSSI involving anaerobic organisms must be excluded from the study, as empiric antibiotics with anti-anaerobic activity are not allowed, and subjects

with suspected or known mycobacterial or fungal ABSSSI are not eligible for study entry (Section 4.2).

The method used for obtaining a microbiological ABSSSI site specimen for Gram stain and culture depends on the ABSSSI type:

- For cellulitis, obtain a specimen by needle aspiration or skin biopsy at the proximal leading edge of erythema, edema, or induration for Gram stain and aerobic bacterial culture.
- For wound infection, obtain a deep-site tissue specimen (e.g., tissue biopsy) or needle aspiration from an area that is physically contiguous with the wound for Gram stain and aerobic bacterial culture.
- For major cutaneous abscess, obtain purulent material during the drainage procedure for Gram stain and aerobic bacterial culture.

Superficial swabs of infected areas are not acceptable, due to the high probability that such specimens could be contaminated with clinically insignificant, and therefore misleading, isolates. However, deep swabs taken during significant surgical interventions are acceptable.

In addition, 2 sets of blood cultures (each consisting of 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). The blood cultures should be obtained before administration of antibacterial therapy, whenever possible. Blood cultures must be repeated every 3 (± 1) days if the previous blood culture was positive, or at any time after screening/baseline if clinically indicated. If the repeat blood culture remains positive with the bacterial pathogen initially isolated, the Investigator must consider modifying the subject's antibiotic therapy and discuss the case with the Medical Monitor.

After screening/baseline, microbiological assessments (ABSSSI site and/or blood cultures) should be repeated only when clinically indicated (e.g., at EOT if study drug is prematurely withdrawn for insufficient clinical effect [clinical failure] at the time of relapse or recurrence after EOT, or if purulence and discharge from the ABSSSI site continues after screening/baseline).

For all microbiological specimens (ABSSSI site and blood), Gram stain, and culture should be performed at the local laboratory according to local standards of care. If bacterial growth occurs from culture, the isolate(s) must be sent to the central laboratory for confirmation of organism identity (to genus and species level) and susceptibility. Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of bacterial isolates.

Antimicrobial susceptibility testing should be performed at the local laboratory according to local standards of care; all clinically significant Gram-positive pathogens should be tested locally for linezolid susceptibility, as appropriate. Note that susceptibility testing for contezolid acefosamil will not be available at the local laboratory. After the cultured isolates are sent to the central laboratory, the central laboratory will test all Gram-positive isolates for both linezolid and

contezolid acefosamil susceptibilities. *Staphylococcus aureus* will also be tested for oxacillin susceptibility as a marker for methicillin resistance by both the central and local laboratories. All clinically significant non-anaerobic Gram-negative isolates will be tested for aztreonam susceptibility by both the central and local laboratories.

The local laboratory should retain all isolates until confirmation of a viable organism is received from the central laboratory. Backup cultures will be requested when the central laboratory does not receive a viable culture, or recovers an organism different from the one recorded by the local laboratory. Refer to the Laboratory Manual for additional details.

8.3 Digital Photography

Documentation of the primary ABSSSI lesion by digital photography will occur at screening/baseline, EA, Day 7, and EOT using the digital camera provided by the Sponsor. Investigators must follow the specific digital photograph procedures that are detailed in the Infection Site Assessment and Measurement Manual and Appendix 7.

9 ASSESSMENT OF EFFICACY

9.1 Clinical Response Definitions

9.1.1 Early Clinical Response

Objective determinations of early clinical response will be made at EA (responder, nonresponder, or indeterminate) as defined in Table 2. Clinical responses will be classified programmatically based on data recorded on the eCRF.

Table 2: Clinical Response Definitions – Early Clinical Response

Timepoint Classification	**Definition**
Early Assessment:	
Responder	Percent reduction in primary ABSSSI lesion size is ≥ 20% compared to baseline Did not receive a non-protocol specified systemic antibacterial agent with activity against Gram-positive organisms for the treatment of ABSSSI Did not die of any cause up to EA
Nonresponder	Percent reduction in primary ABSSSI lesion size is < 20% compared to baseline, or Received a non-protocol specified systemic antibacterial agent with activity against Gram-positive organisms for the treatment of ABSSSI, or Died of any cause up to EA
Indeterminate	Study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up, did not attend the EA clinic appointment)

ABSSSI = acute bacterial skin and skin structure infection; EOT = end of therapy; I & D = incision and drainage; PTE = post therapy evaluation

9.1.2 Investigator's Assessment of Clinical Response

The Investigator's assessment of clinical response at EOT, PTE, and LFU will be classified as defined in Table 3. Investigator assessed clinical failures at EOT will be carried forward as the clinical response at PTE.

Table 3: Clinical Response Definitions – Investigator's Assessment

Timepoint Classification	Definition
EOT and PTE:	
Success	Resolution or near resolution of most baseline ABSSSI signs and symptoms No surgical procedure to treat the infection after 72 hours post-baseline that was not planned at baseline No new signs, symptoms or complications attributable to the ABSSSI No inter-current non-protocol specified systemic antibacterial therapy with activity against Gram-positive organisms for the treatment of ABSSSI Did not die of any cause up to EOT or PTE
Failure	Lack of resolution or near resolution of most baseline ABSSSI signs and symptoms Any surgical procedure to treat the infection > 72 hours post-baseline that was unplanned at baseline New signs, symptoms, or complications attributable to the ABSSSI 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 Died of any cause up to EOT and PTE
Indeterminate	Study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up). No baseline Gram-positive organisms for the treatment of ABSSSI.
LFU:	
Sustained clinical success	No new signs or symptoms of primary ABSSSI after PTE
Clinical relapse/failure	New or worsened signs or symptoms of primary ABSSSI after PTE
Indeterminate	Study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up). No baseline Gram-positive organisms for the treatment of ABSSSI.

ABSSSI = acute bacterial skin and skin structure infection; EA = early assessment; EOT = end of therapy; I & D = incision and drainage; LFU = late follow-up; PTE = post therapy evaluation

Prior to any premature discontinuation of study drug, the study site personnel should notify the Medical Monitor if the subject's medical condition allows.

Data for all subjects will be reviewed to ensure the Investigators are following the protocol defined criteria for clinical response and queries will be issued as needed to clarify any response that does not meet the protocol definition.

9.2 Microbiological Response Definitions

9.2.1 Per-Pathogen Microbiological Response

A microbiological outcome at the PTE visit will be determined in the micro-ITT and ME populations for each pathogen isolated from the ABSSSI site or blood at screening/baseline. Microbiological outcome categories include eradication, presumed eradication, persistence, presumed persistence, and indeterminate, as defined in Table 4. Favorable microbiological outcomes include eradication or presumed eradication. Unfavorable microbiological outcomes include persistence or presumed persistence.

Table 4: Microbiological Outcome Categories

Outcome Category	Definition
Eradication	An adequate source specimen demonstrates absence of the original screening/baseline pathogen
Presumed eradication	An adequate source specimen was not available to culture and the subject was assessed as a clinical success by the Investigator at PTE
Persistence	An adequate source specimen demonstrates continued presence of the original screening/baseline pathogen
Presumed persistence	An adequate source specimen was not available to culture and the subject was assessed as a clinical failure by the Investigator at PTE
Indeterminate	An adequate source specimen was not available to culture and the subject's clinical response was assessed as indeterminate

9.2.2 Per-Subject Microbiological Response

An overall microbiological response at the PTE visit will be determined in the micro-ITT and ME populations for each subject based on individual outcomes for each screening/baseline pathogen. For a subject to have a favorable per-subject microbiological response, the outcome for each screening/baseline pathogen must be favorable (eradicated or presumed eradicated, as defined in Table 4). For a subject to have an unfavorable per-subject microbiological response, the outcome for a screening/baseline pathogen must be unfavorable (persistence, presumed persistence, as defined in Table 4). If the same pathogen is isolated from multiple sites (e.g., blood and ABSSSI site culture), the worst response will be used to determine the per-subject microbiological response.

9.2.3 Emergent Infections

ABSSSI caused by pathogens first appearing after screening/baseline will be categorized as either superinfections or new infections as defined in Table 5.

Table 5: Emergent Infections

Category	Definition
Superinfection	Isolation of a new pathogen(s) (other than the original screening/baseline pathogen[s]) from the primary ABSSSI site and from an appropriate ABSSSI specimen 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 and from an appropriate ABSSSI specimen 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.

ABSSSI = acute bacterial skin and skin structure infection; EOT = end-of-therapy

10 ASSESSMENT OF SAFETY

All subjects will be monitored for the occurrence of AEs throughout the study, including AEs of special interest that are associated with the oxazolidinone class of antibiotics. Electrocardiograms, hematology evaluations, chemistry, coagulation, and UA will be performed at screening/baseline and at various timepoints during and after the dosing period (Table 1). Each recorded AE will be described by its duration (i.e., start and end dates), severity, seriousness, and suspected relationship to the study drug. Adverse events will be graded as mild, moderate, or severe, as detailed in Section 10.1.2_Assessment_of_Severity. Relationship of the AE to study drug will be characterized as related (including possibly related or definitely related) and unrelated, as detailed in Section 10.1.3.

As detailed in Section 3.4, if study drug is determined not to be safe and tolerated, the study drug assignment for those subjects with a significant 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 is 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.

Reports of AEs will be collected for all subjects from the time informed consent is signed. The Investigator will assess all AEs and SAEs and record the following information on the appropriate eCRF page:

- Date and time of onset
- Date of resolution or stabilization
- Severity
- Relationship to study drug
- Action taken with study medication

The Investigator should distinguish between local and systemic AEs. An example of a possible systemic AE includes generalized rash or pruritus related to an allergic reaction. An example of a possible local AE includes a focal rash or irritation that is localized to a cutaneous area surrounding a venous blood draw.

Clinically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory. For example, laboratory workup of an AE of anemia could include iron tests, reticulocyte count, and blood smear, among other local laboratory tests. The Investigator should

employ best medical judgment in determining how to manage AEs and SAEs. Any questions regarding AE or SAE management should be directed to the Medical Monitor.

Prior to any premature discontinuation of study drug or unblinding of study drug assignment, the study site personnel should notify the Medical Monitor if the subject's medical condition allows.

10.1 Adverse Events

10.1.1 Definition

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable or unintended sign, symptom, or disease temporally associated with the use of a drug, without any judgment about causality. Adverse events are collected from the time the informed consent is signed.

An AE does *not* include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that necessitates the procedure is an AE.
- Any pre-existing disease or condition, or laboratory or ECG abnormality, present or detected prior to administration of study drug that does not worsen.
- Laboratory or ECG abnormalities without clinical manifestations, which do not require medical intervention, or that do not result in termination or delay of study medication (see Section 10.2_Reporting_Laboratory_and for further detail).
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social, or convenience admissions).
- Overdose of any study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation.
- Worsening of the primary ABSSSI for which the subject was enrolled.

10.1.2 Assessment of Severity

Severity of AEs will be assessed by the Investigator was mild, moderate, or severe (Table 6). This assessment is subjective and the Investigator should use medical judgment to compare the reported AE to similar types of events observed in clinical practice. It is important to recognize that severity is not equivalent to event seriousness (see Section 10.1.4.2).

Table 6: Guidelines for Severity Assessments

Severity	Definition
Mild	Symptom(s) barely noticeable to the subject, transient, or does (do) not make the subject uncomfortable. The AE does not influence regular, daily performance or functioning (e.g., functioning at work or school). Special treatment (e.g., with a prescription drug) is not ordinarily required for relief of symptom(s).
Moderate	Symptom(s) of a sufficient severity introduce a low level of inconvenience or concern to the subject. The AE may alter regular, daily performance or functioning (e.g., functioning at work or school), but is ameliorated with simple therapeutic measures.
Severe	Symptom(s) of a sufficient severity to cause the subject severe discomfort, interrupt daily activities, or lead to cessation of administration of study drug. Treatment for symptom(s) is needed. A severe AE does not necessarily qualify as an SAE (Section 10.1.4.2).

10.1.3 Relationship to Study Drug

For each reported AE, the Investigator must make an assessment of the relationship of the event to the study drug using the following scale:

- Unrelated: The event is definitely not associated with administration of study drug, and is judged clearly due to causes other than the study drug.
- Possibly related (Suspected Adverse Reaction [SAR]): A causal relationship between the study drug and the AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. This implies a lesser degree of certainty about causality than a definitely related AE. Additional evidence to suggest a SAR includes:
    - Individual occurrences of uncommon AEs that are known to be strongly associated with drug exposure (e.g., angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, Stevens-Johnson Syndrome).
    - One or more occurrences of an AE that is uncommon in the study population, but not commonly associated with drug exposure (e.g., heart valve lesions in young adults, intussusception in healthy infants).
- Definitely Related (Adverse Reaction): A causal relationship between the study drug and the AE is definite.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be unrelated to administration of study drug, then an alternative explanation should be provided.

10.1.4 Serious Adverse Events

An SAE is defined as any adverse experience occurring at any dose of study medication that occurs between the time informed consent is signed and within 30 days after the final administration of study drug that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization (*excluding hospitalization prior to randomization due to initial management of ABSSSI at baseline and new hospitalizations due to progression of the underlying primary ABSSSI lesion*) or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Events that jeopardize the subject sufficiently that medical or surgical intervention may be required to prevent one of the above outcomes (e.g., bronchospasm requiring urgent management in an emergency room, blood dyscrasias that do not result in hospitalization, seizures that do not result in hospitalization)

10.1.4.1 Serious Adverse Event Reporting

The Sponsor has requirements for expedited reporting of SAEs meeting specific criteria to worldwide regulatory authorities. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after administration of study drug. All SAEs must be reported to the Medical Monitor within 24 hours of the investigational site's knowledge of the event.

The study site will transmit a SAE Report (SAER) by email (preferred) or facsimile (backup) to InClin Drug Safety. An initial report can be made via telephone in the case of an urgent event or question, but a completed SAER must still be emailed or faxed within 24 hours of the site's knowledge of the event. The investigational site will be provided with SAER forms wherein the following information is requested. In addition, relevant eCRF pages should be appended to communicate relevant study drug and subject outcome information. The information needed for completing an SAER is as follows:

- Subject identification, Investigator name, and site number.
- SAE information: event term, onset date, severity, and causal relationship.
- The outcomes attributable to the event (e.g., death, a life-threatening AE, inpatient hospitalization, prolongation of existing hospitalization, a persistent or significant disability or incapacity, or other important medical event[s]).

- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history.

- The first and last dates of administration of study drug. NOTE: As this is a double-blind study, SAERs should not indicate specific study drug assignments.

- Indicate if the study drug was discontinued or if the administration of study drug schedule modified.

- Supplemental information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The SAER should be faxed within 24 hours with as much of the above information as available at the time. The following minimum information is required for reporting an SAE: subject identification, reporting source, and an event or outcome. Supplemental information may be transmitted using a follow-up report and should not delay the initial report. The Sponsor may contact the investigational site to solicit additional information or to follow-up on the event.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the eCRF.

10.1.4.2 "Serious" Versus "Severe" Adverse Events

To avoid confusion or misunderstanding over the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided (excerpted from International Council for Harmonisation [ICH] E2A):

The term "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.4.3 SAE Definition Clarifications

- Death is an outcome of an AE, and not an AE in itself.

- All deaths during administration of study drug or occurring within 30 days of the last administration of study drug, regardless of cause or relationship, must be reported using the SAER.

- "Occurring at any dose" does not imply that the subject is actively receiving study drug at the time of the event.

- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, had it occurred with greater severity.

- Complications that occur during hospitalizations are AEs. If an AE prolongs hospitalization, it is an SAE.

- "Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department (although an emergency department visit may define a medically important event, which is also considered an SAE).

- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. In such cases, the diagnosis should be documented as the AE or SAE, rather than as the individual signs or symptoms.

10.1.5 Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an AE that occurs during or after the first administration 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.

10.1.6 Life-threatening Adverse Event

A life-threatening AE is an AE that, in the view of either the Investigator or Sponsor, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

10.1.7 Unexpected Adverse Event

An AE is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Some AEs are listed in the IB as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered unexpected until they have been observed with the drug under investigation.

10.2 Reporting Laboratory and Electrocardiogram Abnormalities

Laboratory and ECG abnormalities should not be recorded as AEs unless they are associated with clinical signs or symptoms, or require medical intervention. However, laboratory and ECG abnormalities (e.g., clinically significant changes detected on clinical chemistry, hematology, UA, etc.) independent from the underlying medical condition that require medical or surgical intervention, or lead to study drug interruption or discontinuation, must be recorded as an AE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than an isolated laboratory or ECG abnormality. In addition, laboratory and ECG abnormalities or other abnormal test assessments that are associated with signs or symptoms must be recorded as AEs if they meet the definition of an AE (or SAE).

10.3 Risks for Women of Childbearing Potential

The risks of treatment with contezolid acefosamil during pregnancy have not been fully evaluated. Therefore, females must be either postmenopausal for ≥2 years or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) or, if of childbearing potential, must have a negative serum or urine pregnancy test (β–HCG) at screening/baseline and be willing to use a highly effective method of contraception throughout the study such as 1 of the following:

- Hormonal contraception (stable dose for 3 months)
- Intrauterine device/intrauterine hormone-releasing system
- Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

Additionally, males (if sexually active and nonsterile) with female partners of childbearing potential must use 2 methods of contraception (i.e., a barrier contraceptive such as condom with spermicidal foam), and be willing to continue to use these same birth control measures while participating in the study (and for 70 days following participation in the study). Males must also refrain from sperm donations during this time.

Female subjects must be instructed to inform the Investigator immediately if they become pregnant during the study. Male subjects must also be instructed to inform the Investigator immediately if a female partner becomes pregnant through at least 70 days (10 weeks) after dosing. In the event of a confirmed pregnancy, the following actions should be taken:

- Study drug should be stopped immediately.
- The pregnancy should be reported to the Medical Monitor within 24 hours of notification using the Pregnancy Report Form.
- The Investigator should counsel the subject regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

- The subject must be monitored until the immediate post-natal period or until termination of the pregnancy. The outcome should be reported to the Medical Monitor using the Pregnancy Outcome Form.

Pregnancy is not an AE, in and of itself. However, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered an SAE and will be reported as described in the AE and SAE sections. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the Medical Monitor.

10.4 Adverse Event Follow-up

All AEs and SAEs will be followed to resolution or stabilization. Adverse events that have not resolved by a study visit, but have stabilized, will be categorized as such in the database. Non-serious AEs that are ongoing at the end of the study will be identified as 'Ongoing'.

10.5 Study Termination or Temporary Suspension

The study may be terminated if significant violations of GCP that compromise the ability to achieve the study objectives or compromise subject safety are observed at any time during the study (Section 4.5). The study may be temporarily suspended or terminated should the Investigator, Sponsor, or IRB determine that the safety of study subjects is significantly jeopardized. The decision for a temporary or permanent study hold will depend on the nature, frequency, and severity of AEs that were observed in all enrolled subjects to date. In a temporary study hold, no additional subjects will be enrolled into the study or dosed with study drug until the study team (including the Investigator and the Medical Monitor) decides it is safe to proceed with the study. The study will be terminated or temporarily suspended if any of the following events occur in a single subject who is receiving active contezolid acefosamil (as determined after unblinding) during the study period:

- Hy's law criteria met; these are defined as elevations of ALT or AST to > 3 times ULN and elevation of serum total bilirubin to ≥ 2 times ULN with serum alkaline phosphatase < 2 times ULN, and no other disease or condition can be found to explain the liver test abnormalities (FDA, 2009)

- Clinically significant cardiac arrhythmia (e.g., Torsade de Pointes)

- Symptomatic anemia with a hemoglobin level < 8.0 g/dL, as confirmed on repeat testing, or requirement for blood transfusion

- Platelet count < 50 x 10^3/mm^3, as confirmed on repeat testing

- WBC count < 2.0 x 10^3/mm^3 or absolute neutrophil count <1,000/mm^3, as confirmed on repeat testing

- Rash defined as an SAE (Section 10.1.4)

- Peripheral or optic neuropathy
- Serotonin syndrome
- Seizure
- Anaphylaxis or allergy-related angioedema

As noted above, safety assessments will be monitored and evaluated on a regular basis by the study team, and any abnormal clinical or laboratory findings or trends will be closely monitored and followed regardless of severity or causality (e.g., before an event reaches a severe grading level or reaches a termination criterion cutoff).

10.6 Data Monitoring Committee

A DMC will not be utilized in this study.

11 ASSESSMENT OF PHARMACOKINETICS

This study will be conducted at multiple clinical sites, and some will have the appropriate equipment and facilities (including refrigerated centrifuges and -70ºC freezers) and experienced personnel to adequately collect, handle, store, and ship PK samples for bioanalysis. PK assessments will only be performed at selected clinical sites with this capability, and PK samples will be obtained from as many subjects as possible at these selected sites. Drug exposure will be predicted based on demographic data (e.g., body weight) for subjects from whom PK samples were not obtained.

- One PK sample after the 1st IV dose (to characterize the loading dose): obtain 1 blood sample between 0.5 to 2 hours after the end of the 1st infusion

- Three PK samples with the 3rd IV dose (to characterize drug exposure and approaching of steady state):

    - Obtain a 1st blood sample (trough level) within 2 hours before the 3rd IV dose

    - Obtain a 2nd blood sample between 0.5 and 3 hours after the end of the 3rd IV dose

    - Obtain a 3rd blood sample between 4 and 11 hours after the end of the 3rd IV dose but before the 4th dose (IV or PO) of study drug.

- Three PK samples at EOT (to evaluate potential drug accumulation):

    - Obtain 1 blood sample (trough level) 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

The PK data acquisition and analysis strategy entail the use of a sparse PK sampling schedule for subjects randomized to contezolid acefosamil. This PK sampling strategy is designed to characterize the impact of the loading dose, and to obtain adequate estimates of drug exposure after the 3rd IV dose and the final dose (IV or PO). Additionally, given the range of demographic data in the expected subject population, these PK data will be used to perform exploratory analyses on the impact of demographic characteristics (e.g., weight, body mass index, age, gender, race) upon the PK (including clearance) of the drug and its metabolites. Only those PK samples collected from subjects randomized to contezolid acefosamil will be analyzed.

The bioanalytical laboratory will measure plasma concentrations of contezolid acefosamil metabolites (MRX-1352, contezolid, and MRX-1320) using validated and sensitive bioanalytical methods. Specific instructions for the collection of plasma drug concentration specimens will be provided in the Laboratory Manual and should be reviewed prior to collection.

When more than one assessment is scheduled at any given timepoint, clinical assessments should precede all blood draws, including ECGs. For subjects managed as outpatients, schedule the clinic visits appropriately to collect PK samples at the end of IV therapy and the EOT visit as described above.

The PK population is defined in Section 12.2. Selected PK samples may be used in the identification of contezolid acefosamil metabolites. Additional details will be provided in the PK Analysis Plan.

12 STATISTICAL METHODS

All data will be summarized separately by study drug (contezolid acefosamil or linezolid). Descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables for each study drug. Frequency distributions (counts and percentages) will be presented for categorical variables. Listings will be provided for individual subject study data.

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized prior to database lock.

12.1 Determination of Study Sample Size

This study is not powered for inferential statistical analysis. Approximately 133 subjects (100 evaluable subjects) in the contezolid acefosamil group and 67 subjects (50 evaluable subjects) in the linezolid group will allow for planning of future studies. 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.

12.2 Analysis Populations

The analysis populations are defined in Table 7, and the relationship between the analysis populations are displayed in Figure 2.

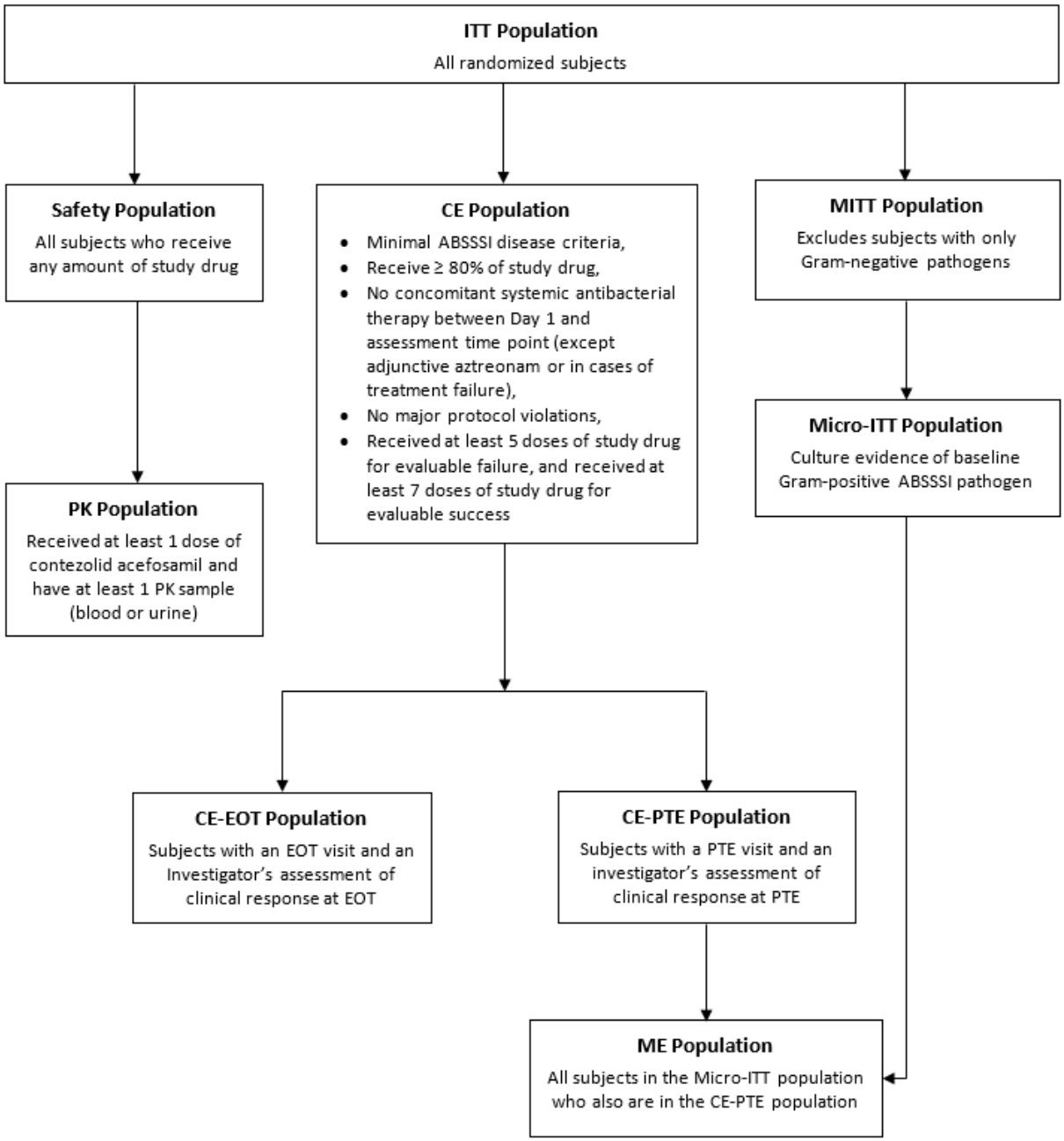
Table 7: Analysis Populations

Analysis Populations	Definitions
ITT Population	All randomized subjects will be included in the ITT population, regardless of whether study drug is administered.
MITT Population	All randomized subjects in the ITT population, excluding subjects with only a Gram-negative pathogen(s) at baseline.
Safety Population	All subjects who receive any amount of study drug will constitute the safety population. Subjects in the safety population will be analyzed according to study drug received.
Micro-ITT Population	All randomized subjects in the ITT population who have culture evidence of a baseline Gram-positive bacterial pathogen known to cause ABSSSI.
CE Populations (CE-EOT, CE-PTE)	All subjects in the ITT population who meet the minimal clinical disease criteria for ABSSSI; receive at least 80% of expected doses based on length of therapy; 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). 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 To be included in the CE-PTE population, the following conditions must be met:

Analysis Populations	Definitions
	• Have an Investigator's assessment of clinical response at PTE (i.e., response can't be indeterminate unless the subject is deemed a clinical failure at the EOT visit) • Had a PTE visit In addition to meeting the above criteria, subjects must meet the following specific conditions to be included in the CE population: • Received at least 5 doses of study drug therapy to be considered an evaluable failure • Received at least 7 doses of study drug therapy to be considered an evaluable success • Did not have any major protocol violation
ME Population	All subjects in the micro-ITT population who also are in the CE-PTE population.
PK Population	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.

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

Figure 2: 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; ME = microbiologically evaluable; micro-ITT = microbiological intent-to-treat; MITT= modified intent-to-treat; PK = pharmacokinetic; PTE = post therapy evaluation

12.3 Determination of Inclusion in Populations

Inclusion in the ITT, safety, and PK populations will be determined programmatically from eCRF data. Inclusion in the MITT and micro-ITT population will be determined by the Medical

Monitor. The Medical Monitor will decide whether each isolate is considered a pathogen. Inclusion in the CE populations will be determined based on a combination of programmatic and manual review by the Medical Monitor. Inclusion in the ME population will be determined programmatically. All manual reviews and determinations of population inclusion/exclusion will be done prior to study unblinding.

12.4 Analysis of Study Populations and Subject Characteristics

Enrollment, study drug administered, premature discontinuations from study medication, withdrawals from the study, and protocol deviations will be summarized by treatment group. A protocol deviation is defined as any variation from the protocol (e.g., enrollment of a subject who did not meet all inclusion and exclusion criteria, failure to perform the assessments and procedures within the required time frame).

Demographics (age, race, sex), description of the baseline ABSSSI type, medical history, and baseline clinical signs and symptoms of ABSSSI will be summarized by treatment group. Baseline pathogens identified at the primary ABSSSI site will also be summarized by treatment group.

The number and percentage of subjects in each population and reasons for exclusion from populations will be listed and summarized by treatment group.

12.5 Study Drug Exposure

By treatment group summaries will be provided for the total number of doses, the number of IV doses, and the number of PO doses. Compliance to study drug will be calculated based on the total number of doses taken, divided by the total number of expected doses.

12.6 Efficacy Analyses

Primary and secondary efficacy evaluations will be summarized by analysis population, as indicated in Table 8.

Table 8: Summary of Primary and Secondary Efficacy Evaluations by Analysis Population

Efficacy Endpoints	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

12.6.1 Primary Efficacy Evaluation

The primary efficacy analysis is an examination of the number of responders in the contezolid acefosamil treated group vs the number 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 (FDA, 2013). Subjects will be programmatically categorized into responders, non-responders or indeterminate based on the eCRF data as previously discussed in Section 9.1.1. Subjects who are lost to follow-up or who have missing data will be classified as indeterminate. The number 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.

12.6.2 Secondary and Additional Efficacy Evaluations

12.6.2.1 Percent Reduction in Lesion Size

Changes from baseline in the percent reduction in lesion area at Day 7 will be summarized by treatment group in the ITT and MITT populations and also by treatment group excluding patients who took non-study antibiotics with the potential to have activity against ABSSSI through the study visit.

12.6.2.2 Clinical Outcomes

Early clinical response at EA will be classified programmatically based on eCRF data as previously discussed in Section 9.1.1. The number and percentage of subjects classified programmatically as a responder, nonresponder, and indeterminate at EA will be tabulated for the populations specified in Table 8 for both treatment groups, and the difference in response rates will be summarized along with the 95% CI for the rate of response.

The Investigator's assessment of clinical response will be classified as previously discussed in Section 9.1.2. The number of subjects with an Investigator's assessment of clinical success, clinical failure, and indeterminate at EOT and PTE will be tabulated for both treatment groups for the populations specified in Table 8 (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 difference in clinical success rates will also be summarized. The 95% CI will be provided for the difference in rates of success at PTE in the ITT and CE-PTE populations only, which are the primary analyses of interest in the EU (EMA, 2013). The durability of clinical response (rate of sustained clinical response and clinical relapse/failure) at LFU will be summarized by treatment group in the micro-ITT and ME populations.

The rates of success as assessed by the CACO (Table 9) will be summarized in the ITT, micro-ITT, and CE-PTE populations. The CACO will be programmatically determined from the programmatic assessment of early clinical response at the EA visit and the Investigator's assessment of clinical response at PTE.

Table 9: Composite Assessment of Clinical Outcome

Early Clinical Response at EA Visit	Investigator's 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

12.6.2.3 Microbiological Outcomes

The number and percentage of subjects with favorable microbiological responses will be summarized at PTE in the ME and micro-ITT populations. Responses include eradication, presumed eradication, persistence, presumed persistence, and indeterminate (Table 4). To have an overall favorable microbiological response, the outcome for each baseline pathogen must be favorable. Of these responses, eradication and presumed eradication will be regarded as a favorable outcome. Persistence and presumed persistence will be regarded as an unfavorable outcome. If a subject has > 1 baseline pathogen, all pathogens must have a favorable response to have overall favorable response. A 2-sided exact 95% CI will be constructed for the percentage of subjects with favorable and non-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 by baseline pathogen will be determined as the proportion of patients with a favorable microbiological response (eradication or presumed eradication) at the PTE visit for each pathogen isolated at baseline from the ABSSSI site. The number and percentage of patients in each treatment group with a microbiologically favorable outcome will be tabulated for the micro-ITT and ME analysis sets.

The number and percentage of subjects in each treatment group with an Investigator's assessment of clinical response of success at the PTE and LFU visit will be tabulated by baseline pathogen in the micro-ITT and ME populations. The number and percentage of subjects in each treatment group who are responders at the EA visit using early clinical response will also be tabulated by baseline pathogen in the micro-ITT population.

Emergent infections (e.g., superinfection, new infection) will not be considered in the microbiological response and will be listed separately (Section 9.2.3).

12.7 Safety Analyses

Evaluation of the safety and tolerability of contezolid acefosamil (IV and PO) q12h (± 2 hours) for 10 to 14 days in the treatment of ABSSSI is an important objective for this Phase 2 study. Safety will be evaluated by presenting summaries of AEs, vital signs, laboratory evaluations (hematology, chemistry, and coagulation), and ECG parameters. For each safety parameter, the last assessment made prior to the first administration of study drug will be used as the baseline for all analyses.

The incidence of TEAEs (defined in Section 10.1.5) will be presented by SOC and PT according to Medical Dictionary of Regulatory Activities (MedDRA®); by SOC, PT, and relationship to study drug; and by SOC, PT, and severity. In addition, the incidence of SAEs and TEAEs leading to discontinuation of study drug will be presented by SOC, PT, and relationship to study drug. If the incidence of SAEs and TEAEs leading to discontinuation of study drug is low, only a listing will be provided.

Descriptive statistics of vital signs at each timepoint measured, as well as the change from baseline and potentially clinically significant changes, will be presented by treatment group. Potentially clinically significant changes will be defined in the SAP. Descriptive statistics for ECGs will also be presented for each timepoint measured. Descriptive statistics for clinical laboratory tests and for the change from baseline will be presented by study visit and treatment group.

12.8 Pharmacokinetic Analyses

Characterization of the population PK of contezolid acefosamil metabolites (IV and PO) q12h (± 2 hours) in the treatment of ABSSSI is an important secondary objective for this study. Plasma samples from subjects in the PK population (Section 12.2) will be analyzed for contezolid acefosamil metabolite concentration (MRX-1352, contezolid, and MRX-1320) using validated and sensitive bioanalytical methods. Key basic PK parameters will be assessed at the end of the first dose of IV therapy, prior to and at 2 timepoints after the end of the third dose of IV therapy, and prior to and after 2 timepoints after the end of the last dose or infusion (IV or PO) at the EOT visit (refer to Section 11 for the timing of the analysis). Only those PK samples collected from subjects randomized to contezolid will be analyzed.

Pharmacokinetic data will be summarized using descriptive statistics and graphically displayed, and population PK modeling analyses will be performed. Further details of the PK sample collection and analyses are provided the PK Analysis Plan and Laboratory Manual.

12.9 Handling of Dropouts, Missing, Unused and Spurious Data

Every effort will be made to collect all data at specified times. For the primary efficacy outcome measure, per-subject clinical response rate at EA in the ITT population, subjects with a missing EA visit will be classified as indeterminate. Missing data for secondary efficacy outcomes will be handled similarly. A detailed description of the handling of drop outs and missing, unused, and spurious data will be provided in the SAP.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Ethical Conduct of Study

This study will be conducted in accordance with applicable United States (US) FDA clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the European Union Directive 2001/20/EC for clinical trials conducted in the European Union, and the IRB/EC/REB and local legal requirements.

13.2 Informed Consent

This study will be conducted in compliance with ICH E6 GCP: Consolidated Guidelines pertaining to informed consent. Subjects will give written consent to participate in the study at the first visit, prior to initiation of any study-related procedure, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. A copy of the informed consent document must be provided to the subject. If applicable, it will be provided in certified translation for non-English-speaking subjects. Signed consent forms must remain in the subject's study file and be available for verification by the Sponsor or representatives of a competent regulatory agency at any time.

13.3 Institutional Review Board Approval

This study will be conducted in compliance with the protocol approved by the IRB and according to ICH and GCP consolidated guidelines and the ethical principles of the Declaration of Helsinki.

No major deviation from the protocol will be implemented without the prior review and approval of the IRB except when it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB for approval. Approval by the IRB of the protocol, informed consent document, and any advertisement used to recruit study subjects must be obtained before the study may be initiated.

The Investigator is responsible for informing the IRB of any changes made to the protocol, and to advise them, at least once a year, about the progress of the study. The Investigator is also responsible for notifying the IRB of any SAEs and significant AEs that occur during the study.

13.4 Investigator Requirements

Each Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor or Sponsor representative must approve any change to the protocol before seeking approval from the IRB. Each Investigator will be responsible for enrolling only those subjects who have met the protocol inclusion and exclusion criteria.

13.5 Electronic Case Report Forms and Data Capture System

This study will be performed using an eCRF. All eCRF data are to be completed by designated site personnel. All data entry, modification, or deletion will be recorded automatically in the electronic audit trail. All electronic data entered by the site (including the electronic audit trail) will be maintained or made available at the site in compliance with 21 CFR Part 11 and other applicable retention regulations.

Before the first subject is dosed at an investigational site, the Sponsor or Sponsor representative will meet with the Investigator and the study center's personnel to train them on recording the data on the eCRFs using an electronic data capture system. The Investigator or designee will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor or Sponsor representative via the system, providing missing or corrected data, and approving all changes performed on the subject data. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature. This electronic signature will be certified as outlined in 21 CFR Part 11. The Sponsor will retain the original eCRF data and audit trail. An electronic or certified paper copy of all completed eCRF data, including query resolution correspondence, will be provided to the Investigator at the end of the study.

Queries may be issued electronically to the clinical study center and answered electronically by that study center's personnel. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable) will be collected.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records.

13.6 Source Data & Document Maintenance

All data collected on the eCRFs must have a source record.

The Investigator agrees by his/her participation that the results of this study may be used for submission to national or international registration. The Sponsor or Sponsor's representative has ethical, legal, and scientific obligations to monitor this study in a detailed and orderly manner in accordance with established research principles and applicable local regulations. As part of a concerted effort to fulfill these obligations, the Sponsor's monitors or representatives will visit the center during the study on a regular basis, in addition to maintaining telephone and written communication.

The Investigator is required to provide the Sponsor with all study data, complete reports, and access to all study records. The Investigator must retain a comprehensive and centralized filing system of all clinical study-related documentation that is suitable for inspection by the Sponsor and representatives of regulatory authorities. The Investigator will allow the Sponsor or its representative, or an appropriate representative of the competent authorities, to inspect all clinical study-related documentation for confirmation of data throughout the study period.

Data generated by this study must be available for inspection by any regulatory authorities, by the Sponsor and by the IRB as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Medical information obtained from subjects during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

13.7 Study Monitoring Requirements

The Sponsor or Sponsor representative will conduct center visits to inspect study data, subjects' medical records, and eCRFs in accordance with current ICH E6 GCP guideline, and the respective US or foreign regulations and guidelines, as applicable. The Sponsor or Sponsor representative will also be able to review query status remotely, which may warrant additional communication with the Investigator and the study center's personnel. The Investigator will make available to the Sponsor, or Sponsor representative, source documents, signed informed consent forms (ICFs), and all other study-related documents.

The Investigator will allow the Sponsor or Sponsor representative and applicable regulatory authorities to inspect facilities and records relevant to this study.

13.8 Study Completion

The Sponsor requires the availability of the following data and materials before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from baseline through LFU for subjects enrolled.
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the Investigator.
- Complete drug accountability records (drug inventory log and an inventory of returned or destroyed clinical material).
- Copies of protocol amendments and IRB approval and notification, if appropriate.
- A summary of the study prepared by the Investigator (an IRB summary letter is acceptable) Trial Conduct & Ethical Considerations.

This study will be conducted in compliance with the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use E6 GCP: Consolidated Guidelines, the ethical principles of the Declaration of Helsinki, FDA GCP guidelines, and any additional IRB-required procedures.

13.9 Quality Control and Quality Assurance

Written standard operating procedures (SOPs) will be followed to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the

protocol, GCP, and the applicable regulatory requirements. Quality control (QC) will be applied to each stage of data handling. Regular monitoring, as defined in ICH GCP, Section 1.8, "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s)", will be conducted throughout the conduct of the study.

The purpose of monitoring is to verify that:

- Rights and well-being of the human subjects are protected;
- The reported study data are accurate, complete, and verifiable from source documents;
- The conduct of the study is in compliance with the currently approved protocol and amendment(s), with GCP, and with the applicable regulatory requirements;
- Monitoring is an integral role in the QC of a clinical trial and is designed to verify the quality of the study.

To fulfill the quality assurance requirements of GCP, audits will be conducted to assess and assure the reliability and integrity of a study's QC systems and recognized standards.

The purpose of an audit is to:

- Ensure subject safety;
- Assure compliance to study protocol procedures, regulatory requirements, and SOPs;
- Assure data quality.

13.10 Retention of Records

Essential documents pertaining to the conduct of this study and the distribution of investigational drugs including eCRFs, ICFs, laboratory test results, and medication inventory records should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of an investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to notify the Investigator/institution as to when these documents no longer need to be retained.

13.11 Finance and Insurance

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

13.12 Publication Policy

The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. The Sponsor will make all reasonable efforts to publish the results of the study in an appropriate peer-reviewed journal. Authorship on the primary publication of the results from this study will be based on contributions to study design, enrollment, data analysis, and interpretation of results.

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Appendix 1. Allowed Prior Antibiotics

Prior (within 96 hours prior to randomization) administration of systemic antibacterial therapy is an exclusion criterion (Section 4.2); however, subjects may be eligible for the study despite prior antimicrobial therapy if they received a single dose of a non-oxazolidinone, short-acting systemic antibiotic within 96 hours prior to randomization. Alternatively, subjects may be eligible despite prior antimicrobial therapy if there is 1) objective clinical evidence of treatment failure such as persistent pain, erythema, induration, and/or purulent drainage (if present) following at least 48 hours of prior, non-study, systemic antibacterial therapy; and 2) 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).

For the purposes of this protocol, short-acting is defined as having a dosage frequency of more than QD. The allowed and disallowed antibacterials listed in Table 10 are based in part from the antimicrobial agents listed in the 2014 Infectious Diseases Society of America (IDSA) Guidelines for the management of skin and soft tissue infections (Stevens, 2014). If a subject received a prior short-acting systemic antibiotic that is not listed here, the Investigator must contact the Medical Monitor to ensure subject eligibility.

Table 10: Allowed and Disallowed Prior Antibiotics in Study MRX4-201

Allowed Antibiotics (One dose within 96 hours prior to randomization)		**Disallowed Antibiotics**
Penicillins:		
Amoxicillin	Nafcillin	NONE
Amoxicillin-Clavulanate	Oxacillin	
Amoxicillin-Sulbactam	Penicillin-G	
Ampicillin	Penicillin-V	
Ampicillin-Sulbactam	Piperacillin	
Dicloxacillin	Piperacillin-Tazobactam	
Cephalosporins:		
Cefaclor	Cefpodoxime	Ceftriaxone
Cefadroxil	Cefprozil	
Cefazolin	Ceftaroline	
Cefdinir	Ceftazidime	
Cefepime	Ceftibuten	
Cefixime	Cefuroxime	
Cefditoren	Cephalexin	
Cefotaxime	Loracarbef	

Allowed Antibiotics (One dose within 96 hours prior to randomization)	Disallowed Antibiotics
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 2. Avoidance of High-Tyramine Foods and Drinks

As linezolid and other oxazolidinones are MAOIs, a significant pressor response has been observed in normal adult subjects receiving linezolid and concomitant tyramine doses of > 100 mg (Zyvox® Prescribing Information, 2018); therefore, subjects receiving linezolid or contezolid acefosamil need to avoid consuming large amounts of foods or beverages with high-tyramine content. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses, fermented or air-dried meats, sauerkraut, soy sauce, and tap beers (Table 11). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.

The following table of high-tyramine foods and drinks to avoid in large amounts during study drug administration in this study has been modified from "Meal Ideas and Menus: Avoiding High-tyramine Foods Made Easy" (Holden, 2006), and serves as a general guidance. Questions as to whether additional foods or beverages must be avoided should be directed to the Medical Monitor.

Table 11: Foods and Beverages to Avoid[a] During Study Drug Administration[b]

Cheeses	Beverages	Meat, Poultry & Fish	Produce	Condiments
Canadian or New York Cheddar Stilton Camembert Swiss Blue/Gorgonzola	Vermouth Tap beer Korean beer	Dry sausages (e.g., mortadella, salami) Chinese dried duck Aged chicken livers Smoked or pickled fish (e.g., lox) Pickled herring Caviar Soups, gravies, or sauces containing meat extracts (e.g., bouillon, beef broth)	Sauerkraut Fava beans and broad beans (Italian green beans) Banana peel Kimchi Miso soup, fermented soy bean/bean curd, tofu	Soy sauce Concentrated yeast extract (Marmite®, Vegemite®) Thai or Vietnamese fish sauce

[a] Similar aged, fermented, pickled, or smoked foods or beverages not shown in this table (e.g., unlisted cheeses or alcoholic beverages) should be generally avoided or consumed rarely with caution.
[b] Foods that need to be avoided from Day 1 until EOT

Appendix 3. Restricted Medications

Oxazolidinones are reversible, nonselective MAOIs; therefore, they have the potential for interaction with adrenergic and serotonergic agents (Zyvox® Prescribing Information, 2018). Exclusion Criterion 17 states that prior (within the past 2 weeks) or expected/required concomitant (from the start of the study drug to EOT) administration of systemic adrenergic or serotonergic medications are excluded (Section 4.2). Such agents include the following:

Adrenergic Agents

Adrenergic agents, including indirect-acting sympathomimetic agents, vasopressors, and dopaminergic agents, should be used with caution when administered concomitantly with oxazolidinones— patients receiving concomitant linezolid may experience a reversible enhancement of the pressor response to such adrenergic agents (Zyvox® Prescribing Information, 2018). Examples of such agents include:

- ***Adrenergic receptor agonists***; examples include dobutamine, dopamine, epinephrine (adrenaline), norepinephrine, phenylpropanolamine, pseudoephedrine
- ***Norepinephrine reuptake inhibitors***; examples include bupropion and methylphenidate
- ***Azapirones***; examples include buspirone and gepirone

Serotonergic Agents

Spontaneous reports of serotonin syndrome, including fatal cases, have been reported with the co-administration of linezolid and serotonergic agents (e.g., antidepressants such as SSRIs). Symptoms and signs of serotonin syndrome include hyperthermia, rigidity, myoclonus, autonomic instability, and mental status changes that include extreme agitation progressing to delirium and coma. In this study, study drug (contezolid acefosamil or linezolid) should not be administered to patients taking any of the following medications:

- ***Serotonin reuptake inhibitors (SSRIs)***; examples include paroxetine, sertraline, fluoxetine, fluvoxamine, and citalopram
- ***Tricyclic antidepressants***; examples include clomipramine and imipramine
- ***Serotonin 5-HT1 receptor agonists*** (***triptans***); examples include almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan

Appendix 4. 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 5. Instructions for Primary ABSSSI Site Measurement

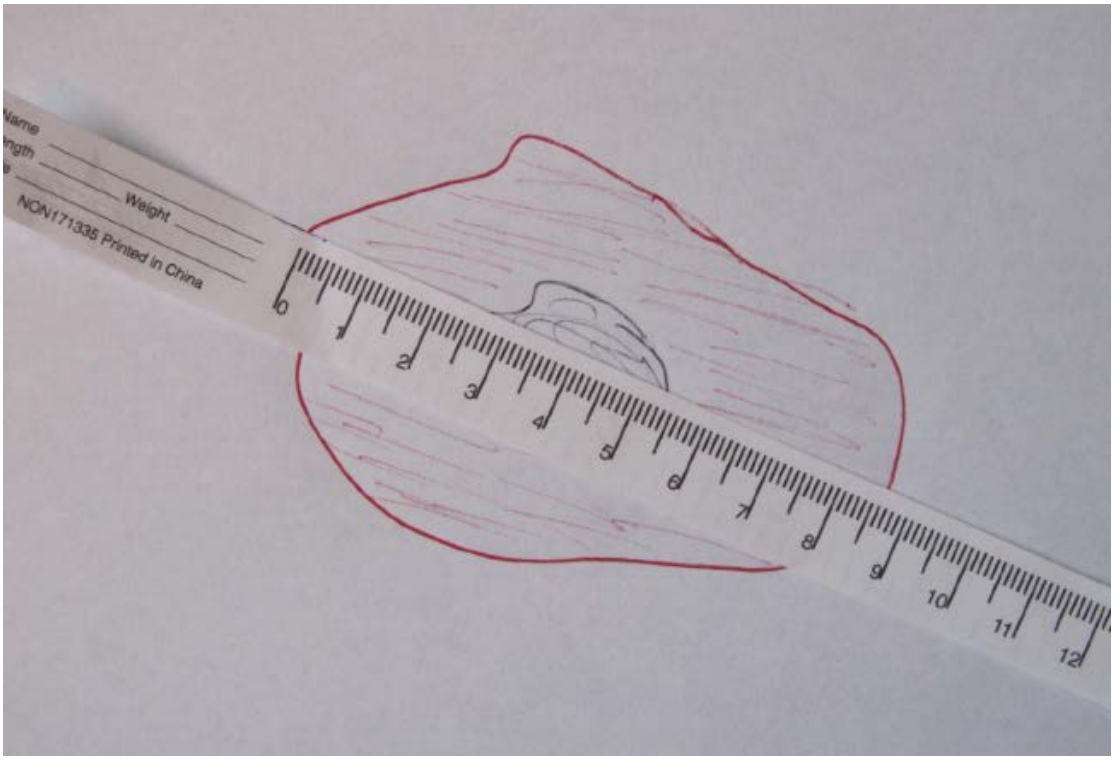
1. Measurements of erythema, edema, or induration, whichever is largest, should be done with a head-to-toe orientation by measuring the longest length head-to-toe and then the widest width perpendicular to that length. Note: the furthest edges of head-to-toe erythema, edema, and/or induration, whichever is largest should be the focus of the measurement. Note: in subjects with darker skin, the perimeter of erythema, edema, and/or induration may be difficult to delineate. Palpation may help delineate the perimeter of the inflammatory lesion.

2. Measure in this manner and document the measurement in the source document and eCRF.

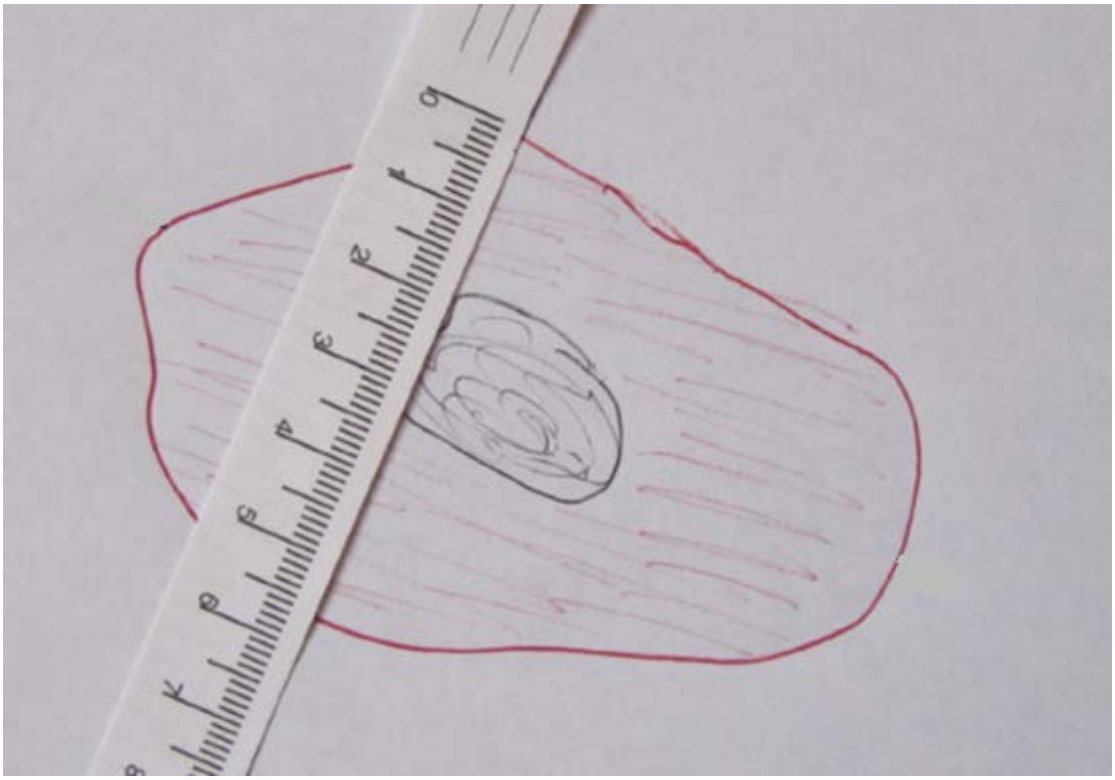
3. A surface area (cm^2) will be calculated by the eCRF.

Figure 3: Primary ABSSSI Site Measurement – Example

Longest length:



Widest width perpendicular:



Appendix 6. 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

Appendix 7. Recommended Instructions for Primary ABSSSI Site Digital Photography

Digital photographs of the primary ABSSSI site will be taken with digital cameras provided by the Sponsor as described below. (IMPORTANT NOTE: Depending upon the location of the infection site on a subject's face or body, a digital image may include certain unique features that could reveal the subject's identity. In order to protect and preserve patient privacy, please obscure or cover any unique features of the subject (such as eyes, nose or tattoos) prior to capturing the digital image.)

1. Drape area behind subject with a white sheet.

2. Place disposable ruler on the skin adjacent to the lesion. Define outer edge of erythema, edema, or induration, whichever is largest, with a marker at each visit.

3. Using the ruler or another piece of paper, place identifying information (date, subject number, body part) adjacent to the lesion.

4. Position camera approximately 2 feet (60 cm) from the lesion.

5. Take a picture at a 90-degree perpendicular angle from the lesion.

6. Do not use any zoom settings.

7. Turn the flash setting to "Off" if enough light is available from other sources. Otherwise, use the flash on auto exposure setting.

8. Use rest of camera's automatic settings for focus and lighting.

9. Place a light source on each side of the subject to help prevent shadows.

10. Capture at least a 4 to 6-inch border around the lesion to assess the status of skin surrounding the lesion. If the lesion wraps around a limb and cannot be fully seen in 1 photograph, take multiple perpendicular photographs to allow documentation of the entire lesion. If multiple photographs are required, mark the top and bottom of the lesion on the subject to indicate the border of the viewing field of each photograph.

11. After the digital photograph is taken, confirm on the camera screen that the picture is clear, in focus, and that all information on the ruler, including the ruler scale, is visible and legible (repeat if necessary).

    a. Please ensure the final image at each visit is saved to the camera's storage card and the storage card is maintained in the study files.

    b. Print the picture and include in the subject's source documents.

    c. In order to protect and preserve patient privacy, please obscure or cover any unique features of the subject (such as eyes, nose or tattoos) that were not able to be covered prior to capturing the digital image.

d. After photographs are taken, discard the paper ruler per institutional guidelines.

The Sponsor may request that digital images be sent to the Sponsor for review. All images from all patients will also be collected on a memory drive or card for storage. Photographic data will be archived and may be analyzed at a later timepoint.