

<b>Official Protocol Title:</b>	Phase 3 Study of IV to Oral 6-Day Tedizolid Phosphate Compared with 10-Day Comparator in Subjects 12 to <18 Years with cSSTI
<b>NCT number:</b>	NCT02276482
<b>Document Date:</b>	26 Feb 2018

**TEDIZOLID PHOSPHATE, SIVEXTRO™ (MK-1986)  
TR701-122 (MK-1986-012)**

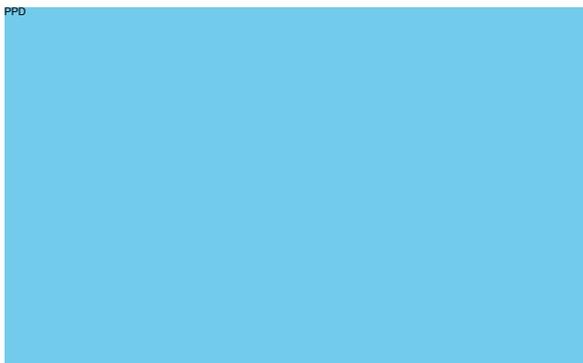
**Phase 3 Study of IV to Oral 6-Day Tedizolid Phosphate  
Compared with 10-Day Comparator in Subjects 12 to  
<18 Years with cSSTI**

IND Number 077872 (TABLET) AND 106307 (IV)  
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Sponsor: Cubist Pharmaceuticals, LLC  
A wholly-owned indirect subsidiary of:  
Merck Sharp & Dohme Corp.  
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Switzerland

Medical Monitor:

Program Lead



Version History:  
Original Protocol 13 August 2014  
Amendment 1: 17 October 2014  
Amendment 2: 13 February 2015  
Amendment 3: 12 April 2016  
Amendment 4: 04 November 2016  
Amendment 5: 25 May 2017  
Amendment 6: 26 Feb 2018

Sponsor Representative:

PPD \_\_\_\_\_ Date

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WHITEHOUSE STATION, NJ, U.S.A.**

26-Feb-2018

**SUMMARY OF CHANGES**

**PRIMARY REASON FOR THIS AMENDMENT:**

Section Number(s)	Section Title(s)	Description of Change	Rationale
Verbatim text is in “quotation marks”; <b>bold type</b> indicates inserted text and <del>strikethrough type</del> indicates deletion.			
1.0 6.1 6.2	Synopsis Overall Study Design Number of Subjects	<p>Changed number of subjects planned to be enrolled from 162 to 120.</p> <p>Changed number of subjects expected to receive tedizolid phosphate and evaluable for the safety analysis from 109 to 86.</p>	<p>Epidemiologic data indicate a decrease in the number of adolescents receiving treatment in acute care settings or being admitted to hospital for acute bacterial skin and skin structure infections (ABSSSI [cSSTI]). In addition, most pediatric patients receiving treatment for ABSSSI in acute care settings or hospitals are younger than those included in this study. These factors have contributed to a slower than expected rate of enrollment in this study.</p> <p>To expedite study completion and provide more timely data to guide treatment for ABSSSI in children, the sample size has been reduced from 162 to 120. This reduces the number of evaluable subjects in the tedizolid group from 109 to 86 subjects. This does not substantially impact the ability to detect common or uncommon adverse events in the evaluable (safety) population. For example, with 86 evaluable subjects in the tedizolid group, the probability of observing an adverse event (AE) with an incidence of <math>\geq 2\%</math> will be <math>\sim 82\%</math>. With the previous sample size (109 evaluable subjects in the tedizolid group), the probability of observing an AE with an incidence of <math>\geq 2\%</math> was similar (<math>\sim 89\%</math>).</p>

**ADDITIONAL CHANGES FOR THIS AMENDMENT:**

<b>Section Number(s)</b>	<b>Section Title(s)</b>	<b>Description of Change</b>	<b>Rationale</b>
Verbatim text is in "quotation marks"; <b>bold type</b> indicates inserted text and <del>striketrough type</del> indicates deletion.			
1.0	Synopsis	Changed estimated date last subject completed from June 2018 to February 2019.	To align with current enrollment expectations.

Section Number(s)	Section Title(s)	Description of Change	Rationale
6.1	Overall Study Design, Table 3: Study Design and Schedule of Assessments	<p>Inserted “<b>by Blinded Investigator</b>” to Table 3 row for assessment of clinical relapse.</p> <p>Edited Table 3 footnote “f” as follows:                      “At the Screening Visit, a local laboratory serum <b>or high sensitivity urine (ie, capable of detecting 10 mIU/mL)</b> test is acceptable for enrollment; send an additional <b>serum</b> sample to the central laboratory. At EOT, a central laboratory serum test is required.”</p> <p>Edited footnote “i” in Table 3 to indicate that cSSTI site specimens are only required after baseline in subjects with no improvement or with deterioration of the primary lesion AND when the lesion is easily accessible.</p> <p>Inserted the following text to Table 3 footnote “o”:                      “<b>The diary should be signed/dated by the individual who enters the data and the site staff who receives the data and reviews it with the subject or guardian.</b>”</p>	<p>To clarify which personnel may perform the assessment of clinical relapse.</p> <p>To clarify pregnancy testing requirements.</p> <p>To clarify which subjects are required to have post-baseline cSSTI site specimens collected. Also, to add detail around how to handle sampling for subjects with multiple lesions.</p> <p>To clarify the process for diary management and ensure diary data can be attributed correctly.</p>



Section Number(s)	Section Title(s)	Description of Change	Rationale
10.5	Lesion Measurements and Assessment of Signs and Symptoms of Disease (investigator blinded to treatment)	<p>Added text to indicate that subjects with no clinical relapse, ongoing AEs, new or ongoing SAEs, or laboratory abnormalities that require an on-site follow-up visit may have the LFU Visit via telephone interview.</p> <p>Added text to indicate unblinded study personnel may ask the subject to rate their level of pain.</p>	<p>This text is repeated from Table 3 to reiterate the conditions for which a telephone interview is acceptable.</p> <p>Pain is a subject-reported outcome and is inherently performed by an unblinded person (the study subject). Therefore, either blinded or unblinded study personnel may ask the subject to rate their pain.</p>
11.2.3	Recording Adverse Events	<p>Made this edit to Paragraph 1:</p> <p>The Investigator will be responsible for ensuring that all AEs occurring during the AE reporting period are reported. The following information is to be recorded for each event <b>and evaluation should be performed by a qualified physician:</b> onset and stop dates, duration, severity, seriousness, causality, action taken, and outcome.</p>	<p>To clarify and ensure alignment with Merck’s standard process for recording adverse events.</p>
11.2.4	Reporting Adverse Events	<p>Made this edit:</p> <p>“...IQVIA (formerly Quintiles)”.</p>	<p>To incorporate the company’s name change.</p>

Section Number(s)	Section Title(s)	Description of Change	Rationale
13.3	Case Report Forms and Study Records	Added definition for 21 CFR Part 11: “The Electronic Data Capture system is validated and conforms to <b>US Code of Federal Regulations, Title 21, Part 11: Electronic Records; Electronic Signatures (21 CFR Part 11)</b> and the Guidance for Industry on Computerizing Systems Used in Clinical Trials requirements.	To identify the standards to which the EDC system is validated; no action needs to be taken by the participating investigators.
15.2	Written Informed Consent	Added definition for 21 CFR Part 50: “The investigator or designee is to explain the study and ICF to the subject and answer any questions in accordance with <b>US Code of Federal Regulations, Title 21, Part 50: Protection of Human Subjects (21 CFR Part 50)</b> and/or applicable laws and regulations.”	To clarify the laws and/or regulations that the investigator complies with when explaining the study and ICF to the subject/legally authorized representative (LAR).
Appendix G	Samples for Pharmacokinetic Assessment	Under Day 7, step 5, changed plasma storage temperature as follows: “5. Collect the supernatant (plasma), split the sample into 2 aliquots and store at <del>-20</del> <b>-70°C (or at up to -20°C; however, -70°C is preferred)</b> <del>or colder</del> ”	To clarify appropriate plasma storage temperature.
Various	Various	Minor typographical or grammatical changes with no effect on study conduct.	To improve clarity or to align with Merck policy.

## INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for tedizolid phosphate. I have read the TR701-122/MK-1986-012 protocol and agree to conduct the study as outlined. I will also ensure that sub investigator(s) and other relevant members of my staff have access to this protocol. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Phase 3 Study of IV to Oral 6-Day Tedizolid Phosphate Compared with 10-Day Comparator in Subjects 12 to <18 Years with cSSTI

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Printed Name of Investigator

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Signature of Investigator

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Date

## 1.0 SYNOPSIS

<b>Name of Sponsor/Company:</b> Cubist Pharmaceuticals, LLC (Cubist), a subsidiary of Merck & Co., Inc.	
<b>Name of Investigational Product:</b> Tedizolid Phosphate	
<b>Name of Active Ingredient:</b> tedizolid phosphate	
<b>Title of Study:</b> Phase 3 Study of IV to Oral 6-Day Tedizolid Phosphate Compared with 10-Day Comparator in Subjects 12 to <18 Years with cSSTI	
<b>Study center(s):</b> This is a multicenter, global study in 30-60 sites.	
<b>Principal Investigator:</b>	
<b>Investigator:</b>	
<b>Study period (years):</b> 3 years Date first subject enrolled: September 2015 Estimated date last subject completed: February 2019	
<b>Phase of development:</b> 3	
<p><b>Objectives:</b></p> <p><b>Primary:</b> The primary objective is to compare the safety of intravenous (IV) and/or oral 6-day 200 mg tedizolid phosphate with 10-day Comparator (IV and/or oral) in subjects 12 to &lt;18 years with complicated skin and soft tissue infection (cSSTI)</p> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>To compare the Blinded Investigator's assessment of clinical success in the tedizolid phosphate and Comparator groups at the Test of Cure (TOC; 18 to 25 days after the first infusion) Visit in the Intent to Treat (ITT) and Clinically Evaluable at TOC (CE-TOC) Analysis Sets</li> <li>To compare the programmatic early clinical response in the tedizolid phosphate and Comparator groups at the 48-72 Hour Visit in the ITT Analysis Set</li> <li>To compare the Blinded Investigator's assessment of clinical success in the tedizolid phosphate and Comparator groups at the End of Therapy (EOT) Visit (Day 11) in the ITT and CE-EOT Analysis Sets</li> </ul>	
<p><b>Methodology:</b> This is a randomized, single-blind, multicenter, Phase 3 study of IV and/or oral tedizolid phosphate 200 mg once per day for 6 days compared with IV and/or oral Comparator for 10 days for the treatment of cSSTI, also known as acute bacterial skin and skin structure infections, in subjects 12 to &lt;18 years. cSSTI includes major cutaneous abscess, cellulitis/erysipelas, and wound infection.</p> <p>Comparator study drugs are provided by the site for both IV and oral administration. For sites that are not permitted by local regulation or otherwise unable to supply the Comparators, Sponsor will arrange the supply of the appropriate comparator drugs. The IV Comparators are vancomycin, linezolid, clindamycin, flucloxacillin, and cefazolin. The oral Comparators are linezolid, clindamycin, flucloxacillin, and cephalexin. Note: Linezolid is allowed as a comparator outside of Europe only. The selection and dose of each Comparator is to be determined by local clinical practice and adjusted as needed for renal impairment.</p>	

26-Feb-2018

At least 50% of subjects will receive all study drug administrations required for a minimum 24-hour period of IV therapy before switching to oral therapy. While many/some subjects may receive IV therapy for the entire treatment duration, a potential switch to oral therapy may occur when the following criteria are met:

- The primary skin lesion has not increased from baseline in area, length, or width
- Last temperature is <37.7°C
- Signs or symptoms of the primary cSSTI site have not worsened and at least 1 has improved from baseline

Intravenous treatment is delivered in a healthcare setting, but a parent/legally-authorized representative (LAR) is allowed to administer oral study drug at home.

Multiple clinical sites will participate in this study. Subjects with a cSSTI caused by suspected or documented gram-positive pathogen(s) at baseline and requiring oral or IV antibiotic therapy will be randomized 3:1 (tedizolid phosphate: Comparator) using an interactive voice response system with randomization stratified by geographic region.

For subjects with major cutaneous abscess or cellulitis/erysipelas, adjunctive antibacterial therapy is prohibited and subjects determined to have gram-negative pathogen causing the cSSTI are excluded from enrollment. Subjects randomized before culture results are available and later determined to have a gram-negative pathogen that requires antibiotic therapy will discontinue study drug and complete assessments for safety.

For subjects with wound infection in countries and/or sites where aztreonam is available, adjunctive aztreonam (IV) and/or metronidazole (IV or oral) may be initiated on Day 1 or during the first 3 days of treatment if the subject is determined or suspected to have an infection with gram-negative aerobic or anaerobic pathogens, respectively. Subjects later determined to have a gram-negative pathogen, but no gram-positive pathogen, will discontinue study drug and complete assessments for safety. In countries and/or sites where IV aztreonam is not available, subjects should not be enrolled if they are known or suspected to have an infection caused by a gram-negative pathogen that will require treatment.

Screening assessments will be performed the calendar day before the first infusion (Day -1) or on the day of the first infusion (Day 1) prior to start of the infusion of study drug. Subjects will be evaluated on Day 1, 48-72 hours after the start of the first infusion, Day 7, EOT (Day 11), TOC (18 to 25 days after the start of first infusion), and at the Late Follow-Up Visit (32 to 39 days after the start of first infusion). Blood samples for pharmacokinetic (PK) analysis will be collected at the Day 1, 48-72 Hour, and Day 7 Visits.

Only the efficacy response evaluator and the evaluator of AE relationship (ie, Blinded Investigator) will be blinded to study treatment.

A Data and Safety Monitoring Board (DSMB) will review safety data including adverse events (AEs), vital signs, physical examinations, and laboratory data when 1/3 and 2/3 of enrollment is completed; additional reviews may be conducted.

The overall duration of the study will be approximately 36 months. Subject participation will be up to 41 days from the Screening Visit to the Late Follow-up Visit, unless a subject is being monitored for a serious AE (SAE). Subjects will be monitored for AEs through 30 days after the last study drug administration and SAEs will be followed using the SAE report form until stabilization, resolution/death, or consent/assent is withdrawn.

Study treatment may be discontinued at the subject's/LAR's request or in the case of unacceptable toxicity.

**Number of subjects (planned):** At least 120 subjects are to be enrolled with at least 86 receiving tedizolid phosphate and evaluable for the safety analysis.

**Criteria for Inclusion**

Subjects who meet all of the following criteria are eligible for the study:

1. Males or females 12 years to <18 years
2. Adequate venous access for IV administration of study drug for at least 24 hours, (for those subjects receiving IV study medication) and for collection of protocol-specified blood samples
3. Local symptoms of acute bacterial infection must have started within 7 days before Study Day -1
4. Subjects that failed prior therapy for the primary infection site (no improvement in signs and symptoms [eg, fever, pain, tenderness, lesion size increasing] after at least 2 full days of antimicrobial therapy) are permitted in the study
5. cSSTI meeting at least 1 of the following clinical syndrome definitions:
  - a. **Cellulitis/erysipelas defined as a diffuse skin infection, characterized by all of the following:**
    - Spreading area of erythema, edema, and/or induration (EEI) extending at least 4 cm in 1 dimension
    - No collection of pus apparent upon visual examination (diagnosis still consistent with cellulitis/erysipelas if pus is collected from the lesion)
    - At least 2 of the following signs of infection:
      - Erythema
      - Induration
      - Swelling/edema
      - Localized warmth
      - Pain or tenderness
    - At least one of the following signs of severe infection:
      - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
      - Presence of lymphangitis
      - Fever, defined as body temperature  $\geq 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) oral or  $38.4^{\circ}\text{C}$  ( $101.1^{\circ}\text{F}$ ) tympanic or rectal (observed by a health care provider)
      - WBC count  $\geq 10,000$  cells/ $\text{mm}^3$  or  $< 4000$  cells/ $\text{mm}^3$
      - $> 10\%$  immature neutrophils
      - Patient-reported pain of at least 6 (Wong-Baker pain scale)

**b. Major cutaneous abscess, defined as an infection characterized by a collection of pus suggested by physical examination that is intradermal or deeper, and is accompanied by the following:**

- EEI extending at least 4 cm in 1 dimension
- At least 2 of the following signs of infection:
  - Erythema
  - Induration
  - Swelling/edema
  - Localized warmth
  - Pain or tenderness
  - Fluctuance
  - Incision and drainage considered or performed
  - Seropurulent drainage
  - Intradermal or subcutaneous fluid collection visualized by ultrasonography, or other radiologic study
- At least one of the following signs of severe infection:
  - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
  - Presence of lymphangitis
  - Fever, defined as body temperature  $\geq 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) oral or  $38.4^{\circ}\text{C}$  ( $101.1^{\circ}\text{F}$ ) tympanic or rectal (observed by a health care provider)
  - WBC count  $\geq 10,000$  cells/ $\text{mm}^3$  or  $< 4000$  cells/ $\text{mm}^3$
  - $> 10\%$  immature neutrophils
  - Patient-reported pain of at least 6 (Wong-Baker pain scale)

**c. Wound infection, defined as an infection characterized by purulent drainage from a wound with surrounding EEI, and further defined by the following:**

- Superficial incision surgical site infection (SSI) meeting all of the following criteria:
  - Follows clean surgery (elective, not emergency, nontraumatic, primarily closed, no acute inflammation; no break in technique; respiratory, gastrointestinal, biliary, and genitourinary tracts not entered)
  - Involves only the skin or subcutaneous tissue around the incision, does not involve fascia
  - Occurs within 30 days after procedure
  - Original surgical incision  $\geq 1$  cm
  - Purulent drainage (spontaneous or therapeutic) or surrounding EEI extending at least 4 cm in 1 dimension

26-Feb-2018

- Or, post-traumatic wound (including penetrating trauma) characterized by purulent drainage (spontaneous or therapeutic) or surrounding EEI extending at least 4 cm in 1 dimension
- At least one of the following signs of severe infection:
  - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
  - Presence of lymphangitis
  - Fever, defined as body temperature  $\geq 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) oral or  $38.4^{\circ}\text{C}$  ( $101.1^{\circ}\text{F}$ ) tympanic or rectal (observed by a health care provider)
  - WBC count  $\geq 10,000$  cells/ $\text{mm}^3$  or  $< 4000$  cells/ $\text{mm}^3$
  - $> 10\%$  immature neutrophils
  - Patient-reported pain of at least 6 (Wong-Baker pain scale)
- 6. Suspected or documented gram-positive infection from baseline Gram stain or culture (see Appendix B). The microbiological sample must have been collected using a valid sampling technique, such as an aspirate, biopsy, incision, deep swab, etc. A superficial swab is not acceptable. Specimens for culture are required for abscesses and wounds at the Screening Visit; specimens for cellulitis are to be collected according to standard practice at the site
- 7. Parent/LAR able to give informed consent and willing and able to comply with all required study procedures. Assent is also required of children who in the Investigator's judgment are capable of understanding the nature of the study

#### Criteria for Exclusion

Subjects who meet any of the following criteria are not eligible to participate in this study:

1. Uncomplicated minor skin and skin structure infections such as pustules, folliculitis, furuncles, minor abscesses (small volume of suppuration not surrounded by cellulitis/erysipelas), impetiginous lesions, superficial or limited cellulitis/erysipelas, and minor wound associated foreign body reactions (eg, "stitch abscesses")
2. cSSTI due to or associated with any of the following:
  - Suspected or documented gram-negative pathogens in subjects with cellulitis/erysipelas or major cutaneous abscess that requires an antibiotic with specific gram-negative coverage. Subjects with wound infections where gram-negative adjunctive therapy is warranted may be enrolled if they meet the other eligibility criteria.
  - Perianal abscess
  - cSSTI within the mouth and/or perioral structures or within the hairline (if this is limits measurements of lesion size)
  - Infections associated with, or in close proximity to, a prosthetic device
  - Concomitant severe acute bacterial infection at another site not including a secondary cSSTI lesion (eg, septic arthritis, endocarditis, osteomyelitis)
  - Infected burns
  - Any rapidly progressing necrotizing process involving deep soft tissue structures (ie, necrotizing fasciitis, pyomyositis)

26-Feb-2018

- Infected human or animal bites
  - Infections at vascular catheter sites or involving thrombophlebitis
  - Incision SSI with any of the following characteristics:
    - Follows clean-contaminated surgery (urgent or emergency case that is otherwise clean, elective opening of respiratory, gastrointestinal, biliary, or genitourinary tract with minimal spillage [eg, appendectomy] not encountering infected urine or bile; minor technique break)
    - Follows contaminated surgery (nonpurulent inflammation; gross spillage from gastrointestinal tract; entry into biliary or genitourinary tract in the presence of infected bile or urine; major break in technique; chronic open wounds to be grafted or covered)
    - Follows surgery in contaminated location (purulent inflammation [eg, abscess]; preoperative perforation of respiratory, gastrointestinal, biliary, or genitourinary tract)
    - Extends into the fascia or muscle layers, organs, or spaces
3. Known bacteremia at the Screening Visit, severe sepsis or septic shock
  4. Recent history of opportunistic infections where the underlying cause of these infections is still active (eg, leukemia, transplant, acquired immunodeficiency syndrome)
  5. Receiving treatment for active tuberculosis
  6. Known or suspected severe neutropenia (absolute neutrophil count  $<500$  cells/mm<sup>3</sup>)
  7. Human immunodeficiency virus positive and CD4 cell counts  $<200$  cells/mm<sup>3</sup> (known or suspected)
  8. Renal impairment requiring peritoneal dialysis, plasmapheresis, hemodialysis, venovenous dialysis, or other forms of renal filtration
  9. Known or suspected severe hepatic impairment
  10. Cardiac or ECG finding which in the opinion of the Investigator would limit the subject's ability to complete and/or participate in this clinical study
  11. Received more than 24 hours of effective antibacterial drug therapy for treatment of the current episode of cSSTI; prior therapy must be short acting (administration frequency is 1 or more doses per 24 hours)
  12. Topical antibacterial ointments or creams applied and remaining on the primary lesion prior to randomization for a duration  $\geq 24$  hours, except for antibiotic/antiseptic-coated dressing applied to the clean postsurgical wound.  
  
Note: As with systemic antibacterial therapy, longer durations of topical treatments *without* apparent effectiveness (see Inclusion Criterion #4: at least 2 full days of treatment without improvement in signs and symptoms) are permitted.
  13. Treatment with investigational medicinal product within 30 days before the first infusion of study drug

26-Feb-2018

14. Investigational device present or removed <30 days before the first infusion of study drug or presence of device-related infection
15. Previous inclusion in the tedizolid phosphate development program
16. Hypersensitivity to tedizolid phosphate or any component in the formulation
17. Hypersensitivity to all of the comparator drugs; hypersensitivity to a comparator drug does not preclude participation if an alternative comparator can be used
18. For subjects with wound infections: history of hypersensitivity to ceftazidime, aztreonam, or any component of the aztreonam formulation, if aztreonam adjunctive therapy is required; history of hypersensitivity to metronidazole or any component of the formulation, if metronidazole adjunctive therapy is required
19. Female subjects who are pregnant or nursing, or who are of childbearing potential and unwilling to use an acceptable method of birth control (eg, abstinence, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel]), or male partner sterilization
20. Subjects and/or LAR who the Investigator considers unlikely to adhere to the protocol, comply with study drug administration, or complete the clinical study
21. Significant or life-threatening condition or organ or system condition or disease (eg, endocarditis, meningitis)
22. Need for oral administration of methotrexate, topotecan, irinotecan or rosuvastatin, during administration of oral study drug.  
  
**Note:** Administration of these concomitant medications during the follow-up period is allowed, as is administration during treatment with *intravenous* tedizolid phosphate.
23. Use of monoamine oxidase inhibitors, tricyclic antidepressants, buspirone, selective serotonin reuptake inhibitors and serotonin 5 hydroxytryptamine receptor agonists (triptans) within 14 days prior to study drug administration

**Investigational product, dosage and mode of administration:**

Subjects will be randomized 3:1 (tedizolid phosphate: Comparator) and receive 6 days of tedizolid phosphate.

- Tedizolid Phosphate for Injection, 200 mg/vial in 250 mL sterile saline for injection infused over 60 minutes once daily
- Tedizolid Phosphate Tablets, 200 mg oral tablet once daily

26-Feb-2018

**Reference therapy, dosage and mode of administration:**

Subjects will be randomized 3:1 (tedizolid phosphate: Comparator) and receive 10 days of Comparator.

Comparator study drugs are provided by the site for both IV and oral administration, with selection and dose determined by local clinical practice. For sites that are not permitted by local regulation or otherwise unable to supply the Comparators, Sponsor will arrange the supply of the appropriate comparator drugs. The IV Comparators are vancomycin, linezolid, clindamycin, flucloxacillin, and cefazolin. The oral Comparators are linezolid, clindamycin, flucloxacillin, and cephalexin. (Note: Linezolid is allowed as a comparator outside of Europe only.)

**Criteria for evaluation**

Safety:

Safety will be assessed through summaries of treatment-emergent AEs, laboratory evaluations (hematology and chemistry), vital signs, physical examinations, visual and neurologic examinations, cSSTI procedures, and concomitant medications.

Other:

Subject assessment of palatability of tedizolid phosphate tablets will be conducted.

The objectives of the population PK analyses are the following:

- To characterize the PK of tedizolid in adolescent subjects, including estimation of typical PK parameters and interindividual and residual variability
- To estimate the effects of individual-specific covariate factors of tedizolid PK in this adolescent population

To provide individual metrics of tedizolid exposure for modeling probabilities of clinical success, microbiological response, or safety outcomes

Efficacy:

The primary efficacy outcome is the Blinded Investigator's assessment of clinical success at the TOC Visit in the ITT and CE-TOC Analysis Sets. A subject assessed as a clinical failure at any time during the study is considered a clinical failure at the TOC Visit.

Secondary efficacy outcomes:

- Programmatic determination of early clinical response at the 48-72 Hour Visit in the ITT Analysis Set. A response of success is  $\geq 20\%$  reduction from baseline lesion area (defined as length x width of the EEI); a response of success would categorize the subject as a responder. A response of failure is a  $< 20\%$  reduction in lesion area; a response of failure would categorize the subject as a non-responder
- Blinded Investigator's assessment of clinical success at the EOT Visit in the ITT and CE-EOT Analysis Sets

Additional efficacy outcomes:

- Change from baseline in lesion size, assessment of signs and symptoms, and regional or systemic signs (lymphadenopathy, temperature, percentage immature neutrophils, white blood cell count)

26-Feb-2018

- Per-pathogen microbiological response at the TOC Visit in the Microbiological ITT (MITT) and Microbiologically Evaluable (ME) Analysis Sets
- Per-subject microbiological response at the TOC Visit in the MITT and ME Analysis Sets
- Blinded Investigator's assessment of clinical success at the TOC Visit in the MITT and ME Analysis Sets
- Per-pathogen Blinded Investigator's assessment of clinical success at the TOC Visit in the MITT and ME Analysis Sets
- Subject Reported Outcome assessment (pain)

**Analysis sets:**

1. ITT: data from randomized subjects
2. Safety: data from randomized subjects who received any amount of active study drug
3. MITT: data from randomized subjects who have a baseline gram-positive bacterial pathogen known to cause cSSTI
4. CE-EOT: data from randomized subjects receiving at least one full infusion of study drug who completed EOT Blinded Investigator's assessments
5. CE-TOC: data from randomized subjects receiving at least one full infusion of study drug who completed EOT and TOC Blinded Investigator's assessments
6. ME: data from subjects in the MITT Analysis Set who are also in the CE-TOC Analysis Set

**Statistical methods:**

The primary objective of the study is to determine the safety of tedizolid phosphate. Thus, the study is not powered for inferential statistics. Rather, a sufficient number of subjects are being enrolled to provide an initial characterization of the safety of tedizolid phosphate in subjects 12 to <18 years of age.

The incidence of treatment-emergent AEs will be presented by System Organ Class and preferred term according to the Medical Dictionary for Regulatory Activities, relationship to study drug, and severity for all subjects. Descriptive statistics of clinical laboratory results (hematology and chemistry), vital sign measurements, and the change from baseline will be presented, as will a summary of laboratory information.

The number and percentage of subjects who have a Blinded Investigator's assessment of clinical success, clinical failure, and indeterminate response at TOC in the ITT and CE-TOC (by definition, subjects in the CE-TOC Analysis Set cannot have an indeterminate response) Analysis Sets will be determined for each treatment group. An exact two-sided 95% confidence interval (CI) will be determined for the rate of early clinical response in each treatment group using the Clopper-Pearson method. The difference in the rate of clinical success will be determined as will a two-sided 95% CI for the difference using the unstratified method of Miettinen and Nurminen. Descriptive statistics, exact two-sided 95% CIs for the point estimates of response and success, and two-sided 95% CIs for the difference in response and success will also be provided for the secondary outcome measures of programmatic determination of clinical response at the 48-72 Hour Visit in the ITT Analysis Set, and the Investigator assessment of clinical response at EOT in the ITT and CE-EOT Analysis Sets.

26-Feb-2018

Additional efficacy analyses will be conducted to support the efficacy findings of the primary and secondary efficacy outcomes. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided.

## 2.0 TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

### TABLE OF CONTENTS

<b>SUMMARY OF CHANGES</b> .....	<b>2</b>
<b>INVESTIGATOR’S AGREEMENT</b> .....	<b>8</b>
<b>1.0 SYNOPSIS</b> .....	<b>9</b>
<b>2.0 TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES</b> .....	<b>19</b>
<b>3.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS</b> .....	<b>25</b>
<b>4.0 INTRODUCTION</b> .....	<b>27</b>
<b>5.0 TRIAL OBJECTIVES AND PURPOSE</b> .....	<b>29</b>
<b>5.1 Primary Objective</b> .....	<b>29</b>
<b>5.2 Secondary Objectives</b> .....	<b>29</b>
<b>5.3 Additional Objectives</b> .....	<b>29</b>
<b>5.4 Additional Efficacy Outcomes</b> .....	<b>29</b>
<b>6.0 INVESTIGATIONAL PLAN</b> .....	<b>30</b>
<b>6.1 Overall Study Design</b> .....	<b>30</b>
<b>6.2 Number of Subjects</b> .....	<b>36</b>
<b>6.3 Treatment Assignment</b> .....	<b>36</b>
<b>7.0 SELECTION AND WITHDRAWAL OF SUBJECTS</b> .....	<b>36</b>
<b>7.1 Subject Inclusion Criteria</b> .....	<b>36</b>
<b>7.2 Subject Exclusion Criteria</b> .....	<b>39</b>
<b>7.3 Subject Withdrawal Criteria</b> .....	<b>41</b>
7.3.1 Subject Withdrawal From the Study.....	41
7.3.2 Discontinuation of Treatment .....	42
7.3.3 Study Discontinuation.....	43
<b>8.0 TREATMENT OF SUBJECTS</b> .....	<b>43</b>
<b>8.1 Description of Study Drug</b> .....	<b>43</b>
<b>8.2 Assessment for IV to Oral Switch</b> .....	<b>44</b>
<b>8.3 Concomitant Medications</b> .....	<b>44</b>
<b>8.4 Treatment Compliance</b> .....	<b>47</b>

<b>8.5</b>	<b>Randomization and Blinding</b> .....	<b>47</b>
<b>9.0</b>	<b>STUDY DRUG MATERIALS AND MANAGEMENT</b> .....	<b>47</b>
<b>9.1</b>	<b>Study Drug</b> .....	<b>47</b>
<b>9.2</b>	<b>Study Drug Packaging and Labeling</b> .....	<b>48</b>
<b>9.3</b>	<b>Study Drug Storage</b> .....	<b>48</b>
<b>9.4</b>	<b>Study Drug Preparation</b> .....	<b>48</b>
<b>9.5</b>	<b>Administration</b> .....	<b>49</b>
<b>9.6</b>	<b>Study Drug Accountability</b> .....	<b>49</b>
<b>9.7</b>	<b>Study Drug Handling and Disposal</b> .....	<b>50</b>
<b>10.0</b>	<b>ASSESSMENT OF EFFICACY</b> .....	<b>50</b>
<b>10.1</b>	<b>Assessment of Efficacy Variables</b> .....	<b>50</b>
<b>10.2</b>	<b>Response Definitions</b> .....	<b>51</b>
10.2.1	Clinical Response Definitions.....	51
10.2.2	Microbiological Response Definitions.....	53
<b>10.3</b>	<b>Evaluability Review Team</b> .....	<b>54</b>
<b>10.4</b>	<b>Sample Collection for Microbiology Assessment</b> .....	<b>54</b>
<b>10.5</b>	<b>Lesion Measurements and Assessment of Signs and Symptoms of Disease (Investigator Blinded to Treatment)</b> .....	<b>55</b>
<b>10.6</b>	<b>Samples for Pharmacokinetic Assessment</b> .....	<b>56</b>
<b>11.0</b>	<b>ASSESSMENT OF SAFETY</b> .....	<b>56</b>
<b>11.1</b>	<b>Safety Parameters</b> .....	<b>56</b>
11.1.1	Samples for Laboratory Evaluation for Safety .....	56
<b>11.2</b>	<b>Adverse and Serious Adverse Events</b> .....	<b>57</b>
11.2.1	Definition of Adverse Events.....	57
11.2.2	Relationship to Study Drug.....	59
11.2.3	Recording Adverse Events.....	60
11.2.4	Reporting Adverse Events .....	60
<b>11.3</b>	<b>Pregnancy</b> .....	<b>61</b>
<b>12.0</b>	<b>STATISTICS</b> .....	<b>62</b>
<b>12.1</b>	<b>Analysis Sets</b> .....	<b>62</b>
12.1.1	Process for Determining Inclusion in Analysis Sets .....	63

<b>12.2</b>	<b>Sample Size</b> .....	<b>63</b>
<b>12.3</b>	<b>General Statistical Considerations</b> .....	<b>63</b>
12.3.1	Subject Population and Characteristics.....	64
12.3.2	Study Drug Exposure .....	64
<b>12.4</b>	<b>Efficacy Analyses (Primary, Secondary, Additional)</b> .....	<b>64</b>
12.4.1	Primary Efficacy Analysis .....	64
12.4.2	Secondary Efficacy Analyses.....	65
12.4.3	Additional Efficacy Analyses .....	65
<b>12.5</b>	<b>Safety Analyses</b> .....	<b>65</b>
12.5.1	Adverse Events .....	65
12.5.2	Laboratory Evaluations .....	65
12.5.3	Handling of Missing Data.....	66
12.5.4	Protocol Deviations.....	67
<b>13.0</b>	<b>DIRECT ACCESS TO SOURCE DATA/DOCUMENTS</b> .....	<b>67</b>
<b>13.1</b>	<b>Study Monitoring</b> .....	<b>67</b>
<b>13.2</b>	<b>Audits and Inspections</b> .....	<b>68</b>
<b>13.3</b>	<b>Case Report Forms and Study Records</b> .....	<b>68</b>
<b>13.4</b>	<b>Institutional Review Board/Ethics Committee/Research Ethics Board</b> .....	<b>69</b>
<b>14.0</b>	<b>QUALITY CONTROL AND QUALITY ASSURANCE</b> .....	<b>69</b>
<b>15.0</b>	<b>ETHICS</b> .....	<b>70</b>
<b>15.1</b>	<b>Ethical Conduct of the Study</b> .....	<b>70</b>
<b>15.2</b>	<b>Written Informed Consent</b> .....	<b>70</b>
<b>15.3</b>	<b>Subject Confidentiality</b> .....	<b>70</b>
<b>16.0</b>	<b>DATA HANDLING AND RECORDKEEPING</b> .....	<b>71</b>
<b>16.1</b>	<b>Inspection of Records</b> .....	<b>71</b>
<b>16.2</b>	<b>Retention of Records</b> .....	<b>71</b>
<b>17.0</b>	<b>PUBLICATION POLICY</b> .....	<b>72</b>
<b>18.0</b>	<b>REFERENCE LIST</b> .....	<b>72</b>
<b>19.0</b>	<b>APPENDICES</b> .....	<b>73</b>

<b>APPENDIX A. SITE INTRUCTIONS FOR PRIMARY cSSTI SITE MEASUREMENT.....</b>	<b>74</b>
<b>APPENDIX B. MICROBIOLOGICAL SAMPLING AND PATHOGEN DETERMINATION .....</b>	<b>75</b>
<b>APPENDIX C. NEUROLOGIC AND CRANIAL NERVE EXAMINATION* .....</b>	<b>77</b>
<b>APPENDIX D. PAIN EVALUATION.....</b>	<b>78</b>
<b>APPENDIX E. SIGNS AND SYMPTOMS OF cSSTI.....</b>	<b>79</b>
<b>APPENDIX F. CLINICAL LABORATORY EVALUATIONS .....</b>	<b>80</b>
<b>APPENDIX G. SAMPLES FOR PHARMACOKINETIC ASSESSMENT .....</b>	<b>81</b>
<b>APPENDIX H. PALATABILITY SCALE.....</b>	<b>82</b>
<b>APPENDIX I. EXAMPLES OF PROHIBITED CONCOMITANT MEDICATIONS .....</b>	<b>83</b>

## LIST OF TABLES

Table 1:	Abbreviations and Definitions of Terms .....	25
Table 2:	Pediatric Studies .....	28
Table 3:	Study Design and Schedule of Assessments .....	33
Table 4:	Concomitant Therapy Rules .....	46
Table 5:	Blinded Investigator's Assessment of Clinical Response Definitions (EOT, TOC Visits) .....	52
Table 6:	Programmatic Assessment of Clinical Response Definitions (48- 72 Hour Visit) .....	53
Table 7:	Blinded Investigator's Assessment of Clinical Relapse Definitions (Late Follow-up Visit) .....	53
Table 8:	Microbiological Response Definitions .....	54
Table 9:	Microbiological Response Definitions: Superinfection or New Infection .....	54
Table 10:	Samples for Microbiology Assessments .....	55
Table 11:	Samples for Safety Laboratory Assessments .....	57
Table 12:	Analysis Sets .....	62
Table 13:	Blinded Investigator's Assessment of Clinical Response Determination Considering Missing Data .....	66

**LIST OF FIGURES**

Figure 1: Study Design and Schedule of Assessments .....32  
Figure 2: Assessment for IV to Oral Switch.....44  
Figure 3: Analysis Sets .....63

### 3.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

Abbreviation or Term	Explanation
ABSSSI	Acute bacterial skin and skin structure infections
AE	Adverse event
BSA	Body surface area
CA	Community-acquired
CE	Clinically evaluable
CFR	Code of Federal Regulations
CI	Confidence interval
CRO	Contract Research Organization
cSSTI	Complicated skin and soft tissue infection
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
EC	Ethics Committee
ECG	Electrocardiogram
e-CRF	Electronic case report form
EI	Erythema, edema, and/or induration
EMA	European Medicines Agency
ERT	Evaluability Review Team
EOT	End of Therapy
EU	European Union
FDA	Food and Drug Administration
FRS	Faces rating scale
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LAR	Legally-authorized representative
LFU	Late Follow-up
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Microbiological Intent to Treat
MRSA	Methicillin-resistant <i>S. aureus</i>
PDCO	Pediatric Committee
PK	Pharmacokinetic

<b>Abbreviation or Term</b>	<b>Explanation</b>
REB	Research Ethics Board
SAE	Serious adverse event
SAP	Statistical analysis plan
SSI	Surgical site infection
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TOC	Test of Cure
US	United States of America
WBC	White blood cell

#### 4.0 INTRODUCTION

Tedizolid phosphate (MK -1986, TR-701 FA) is a novel oxazolidinone prodrug antibiotic that is rapidly converted in vivo by phosphatases to the microbiologically active moiety tedizolid (TR-700). Tedizolid is a protein synthesis inhibitor that interacts with the 50S subunit of the bacterial ribosome. Tedizolid has bacteriostatic activity against gram-positive bacteria including common skin pathogens *Staphylococcus aureus* (both methicillin-sensitive and –resistant strains) and *Streptococcus pyogenes*, less common species causing acute bacterial skin and skin structure infections (ABSSSI), *S. anginosus-milleri* group and *Enterococcus faecalis*, and other gram-positive aerobes and anaerobes. Tedizolid phosphate has been approved for the treatment of adults with ABSSSI in multiple countries and regions including the United States and the European Union.

Two registrational Phase 3 studies in patients with ABSSSI found 6 days treatment with 200 mg per day tedizolid phosphate to be noninferior to 10 days treatment with 600 mg twice daily linezolid at 48 to 72 hours based on no increase in lesion area from baseline and no fever (Study TR701-112) or a 20% decrease in lesion area from baseline (TR701-113). Patients in

TR701-112 were required to be at least 18 years of age, while patients in TR701-113 could be as young as 12 years, although only 2 adolescents were enrolled in the trial. The change in the age criteria for eligibility from the TR701-112 study to the second TR701-113 study was based on pharmacokinetic (PK) and safety data from Study TR701-111 in adolescents. One adolescent received tedizolid phosphate in TR701-113 and was considered a clinical success and experienced no treatment-emergent adverse events (TEAEs).

In the Phase 1 TR701-111 study, 20 adolescents (12 to 17 years old) who were receiving prophylaxis for or had a confirmed or suspected gram-positive infection for which they were receiving treatment with gram-positive activity received tedizolid phosphate. Results of the PK analysis showed that the mean  $C_{max}$  and  $AUC_{0-\infty}$  for oral or intravenous (IV) administration of tedizolid 200 mg were similar in adolescent and in healthy adult subjects, thus the adult dose of 200 mg tedizolid phosphate is an appropriate dose to further evaluate in adolescents. In this study, TEAEs were mild, no subjects discontinued treatment due to an adverse event (AE), and no deaths or serious AEs (SAEs) were reported. Clinical laboratory evaluations, vital sign measurements, physical examinations, and electrocardiograms (ECGs) did not show clinically significant changes.

As with adults, *S. aureus*, *Streptococcus A group*, and *Enterococcus* species are the most common pathogens in pediatric ABSSSIs. The recent emergence of community-acquired (CA) staphylococcal skin infections is particularly troublesome in the pediatric population and both hospital-acquired and CA-MRSA (methicillin-resistant *S. aureus*) are more common among children in summer and autumn months than in winter or spring. Antibiotic choices for ABSSSI in adults and children are similar, with the exception of linezolid, an oxazolidinone, which is not approved for pediatric use in the European Union (EU).

The EMA/Paediatric Committee (PDCO) issued a Pediatric Investigation Plan Positive Opinion in October 2013 for the treatment of complicated skin and soft tissue infections (cSSTIs). The proposed FDA Pediatric Study Plan was submitted with the new drug

applications in October 2013, and reflects the outcome of the EMA/PDCO discussions and meetings with the FDA. These studies are described in [Table 2](#).

Table 2. Pediatric Studies

Study	Description
<b>Completed</b>	
Phase 1 PK TR701-111	Open-label, multicenter, two-part, single-dose, parallel-design, safety, and pharmacokinetic study of oral and IV TR-701 FA in subjects 12 to 17 years
<b>Ongoing</b>	
TR701-122 (MK-1986-012)	Phase 3 study of IV to oral 6-day tedizolid phosphate compared with 10-day comparator in subjects 12 to <18 years with cSSTI
TR701-120 (MK-1986-013)	Phase 1, single-dose safety and pharmacokinetic study of oral and IV tedizolid phosphate in in-patients 2 to <12 Years
<b>Planned</b>	
TR701-128 (MK-1986-018)	Randomized, single-blind, safety and efficacy study of IV to oral tedizolid phosphate and comparator for cSSTI in subjects >3 months to <12 years
TR701-121 (MK-1986-014)	Phase 1, single-dose safety and pharmacokinetic study of oral and IV tedizolid phosphate in in-patients under 2 years
TR701-129 (MK-1986-021)	Open-label, multicenter, Phase 3 study of IV tedizolid phosphate 5 mg/kg once daily for 10 to 14 days for hospital-acquired late-onset sepsis in preterm and term neonates and infants aged 5 days to ≤3 months

Abbreviations: cSSTI=complicated skin and soft tissue infection; IV=intravenous.

Results of Study TR701-111 established that exposure was similar in adults and adolescents and that tedizolid phosphate was well-tolerated with no clinically significant safety findings in 20 adolescent subjects. This amended study is a randomized, multicenter, Phase 3 study of IV and/or oral tedizolid phosphate 200 mg once per day for 6 days compared with IV and/or oral Comparator for 10 days for the treatment of cSSTI, also known as ABSSSI, in subjects 12 to <18 years.

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with applicable United States FDA clinical trial regulations and guidelines, the International Conference of Harmonisation (ICH; E6) Good Clinical Practice (GCP) guidelines and E11 Clinical Investigation of Medicinal Products in the Paediatric Population, the EU Directive 2001/20/EC for clinical trials conducted in the EU, and the Institutional Review Board (IRB)/Ethics Committee (EC)/Research Ethics Board (REB) and local legal requirements.

## **5.0 TRIAL OBJECTIVES AND PURPOSE**

### **5.1 Primary Objective**

The primary objective is to compare the safety of IV and/or oral 6-day 200 mg tedizolid phosphate with 10-day Comparator in subjects 12 to <18 years with cSSTI.

### **5.2 Secondary Objectives**

- To compare the Blinded Investigator's assessment of clinical success in the tedizolid phosphate and Comparator groups at the Test of Cure (TOC; 18 to 25 days after the first infusion) Visit in the Intent to Treat (ITT) and Clinically Evaluable at TOC (CE-TOC) Analysis Sets
- To compare the programmatic early clinical response in the tedizolid phosphate and Comparator groups at the 48-72 Hour Visit in the ITT Analysis Set
- To compare the Blinded Investigator's assessment of clinical success in the tedizolid phosphate and Comparator groups at the End of Therapy (EOT) Visit (Day 11) in the ITT and CE-EOT Analysis Sets

### **5.3 Additional Objectives**

- To compare the microbiological outcomes in the tedizolid phosphate and Comparator groups at the TOC Visit in the Microbiological ITT (MITT) and Microbiologically Evaluable (ME) Analysis Sets
- Subject assessment of palatability of tedizolid phosphate tablets
- The objectives of the population PK analyses are the following:
  - To characterize the PK of tedizolid in adolescent subjects, including estimation of typical PK parameters and inter-individual and residual variability
  - To estimate the effects of individual-specific covariate factors of tedizolid PK in this adolescent population
  - To provide individual metrics of tedizolid exposure for modeling probabilities of clinical success, microbiological response, or safety outcomes

### **5.4 Additional Efficacy Outcomes**

- Change from baseline in lesion size, assessment of signs and symptoms, and regional or systemic signs (lymphadenopathy, temperature, percentage immature neutrophils, white blood cell [WBC] count)
- Per-pathogen microbiological response at the TOC Visit in the MITT and ME Analysis Sets

26-Feb-2018

- Per-subject microbiological response at the TOC Visit in the MITT and ME Analysis Sets
- Blinded Investigator's assessment of clinical success at the TOC Visit in the MITT and ME Analysis Sets
- Per-pathogen Blinded Investigator's assessment of clinical success at the TOC Visit in the MITT and ME Analysis Sets
- Subject Reported Outcome assessment

## **6.0 INVESTIGATIONAL PLAN**

### **6.1 Overall Study Design**

This is a randomized, single-blind, multicenter, Phase 3 study of IV and/ or oral tedizolid phosphate 200 mg once per day for 6 days compared with IV and/or oral Comparator for 10 days for the treatment of cSSTI, also known as acute bacterial skin and skin structure infections, in subjects 12 to <18 years. cSSTI includes major cutaneous abscess, cellulitis/erysipelas, and wound infection.

Comparator study drugs are provided by the site for both IV and oral administration. The IV Comparators are vancomycin, linezolid, clindamycin, flucloxacillin, and cefazolin. The oral Comparators are linezolid, clindamycin, flucloxacillin, and cephalexin. (Note: Linezolid is allowed as a comparator outside of Europe only.) The selection and dose of each Comparator is to be determined by local clinical practice and adjusted as needed for renal impairment.

At least 50% of subjects will receive all study drug administrations required for a minimum 24-hour period of IV therapy before switching to oral therapy. While subjects may receive IV therapy for the entire treatment duration, the optional switch to oral therapy may occur when the following criteria are met:

- The primary skin lesion has not increased from baseline in area, length, or width
- Last temperature is <37.7°C
- Signs or symptoms of the primary cSSTI site have not worsened and at least 1 has improved from baseline

Intravenous treatment is delivered in a healthcare setting, but a parent/legally-authorized representative (LAR) is allowed to administer oral study drug at home.

Multiple clinical sites will participate in this study. Subjects with a cSSTI caused by suspected or documented gram-positive pathogen(s) at baseline and requiring oral or IV antibiotic therapy will be randomized 3:1 (tedizolid phosphate: Comparator) using an interactive voice response system with randomization stratified by geographic region.

For subjects with major cutaneous abscess or cellulitis/erysipelas, adjunctive antibacterial therapy is prohibited and subjects determined to have gram-negative pathogen causing the cSSTI are excluded from enrollment. Subjects randomized before culture results are

available and later determined to have a gram-negative pathogen that requires antibiotic therapy will discontinue study drug and complete assessments for safety.

For subjects with wound infection:

- In countries and/or sites where aztreonam is available, adjunctive aztreonam (IV) and/or metronidazole (IV or oral) may be initiated on Day 1 or during the first 3 days of treatment if the subject is determined or suspected to have an infection with gram-negative aerobic or anaerobic pathogens, respectively. Subjects later determined to have an infection caused by a gram-negative pathogen, but no gram-positive pathogen, will discontinue study drug and complete assessments for safety.
- In countries where IV aztreonam is not available, subjects should not be enrolled if they are known or suspected to have a gram-negative pathogen that will require treatment.

Screening assessments will be performed the calendar day before the first infusion (Day -1) or on the day of the first infusion (Day 1) prior to start of the infusion of study drug. Subjects will be evaluated on Day 1, 48-72 hours after the start of the first infusion, Day 7, EOT (Day 11), TOC (18 to 25 days after the start of first infusion), and at the Late Follow-Up Visit (32 to 39 days after the start of first infusion). Blood samples for PK analysis will be collected at the Day 1, 48-72 Hour, and Day 7 Visits. See [Figure 1](#).

Only the efficacy response evaluator and the evaluator of AE relationship (ie, Blinded Investigator) will be blinded to study treatment.

A Data and Safety Monitoring Board (DSMB) will review safety data including AEs, vital signs, physical examinations, and laboratory data when 1/3 and 2/3 of enrollment is completed; additional reviews may be conducted.

The overall duration of the study will be approximately 36 months. Subject participation will be up to 41 days from the Screening Visit to the Late Follow-up Visit, unless a subject is being monitored for an SAE. Subjects will be monitored for AEs through 30 days after last study drug administration and SAEs will be followed using the SAE report form until stabilization, resolution/death, or consent/assent is withdrawn. Study treatment may be discontinued at the subject's/LAR's request or in the case of unacceptable toxicity.

At least 120 subjects are to be enrolled with at least 86 receiving tedizolid phosphate and evaluable for the safety analysis.

Figure 1: Study Design and Schedule of Assessments

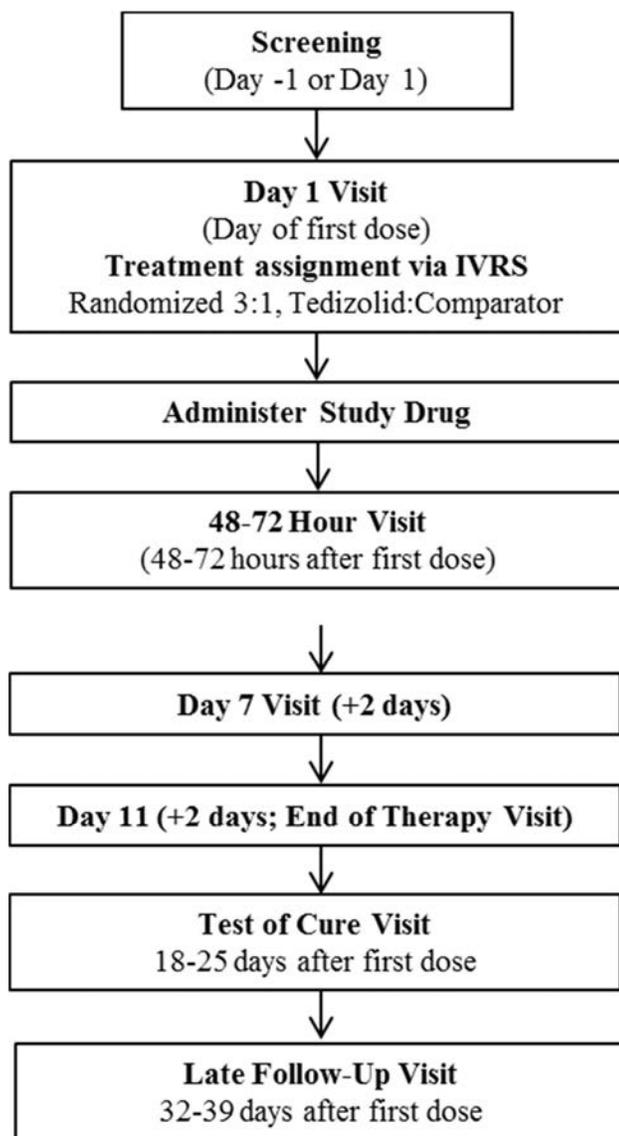


Table 3: Study Design and Schedule of Assessments

<b>Study Procedures</b>	<b>Screening</b> (Day -1 or Day 1; day of infusion or previous calendar day)	<b>Day 1</b>	<b>48-72 Hours</b>	<b>Day 7 (+2)</b>	<b>EOT (Day 11+2)</b>	<b>TOC</b> (18 to 25 days after first dose of study drug)	<b>Late Follow-Up<sup>a</sup></b> (32 to 39 days after first dose of study drug)
Collect informed consent (before any procedures)	x						
Verify subject meets inclusion and not exclusion criteria	x						
Record medical and surgical history	x						
Record height and weight, calculate body surface area	x						
Collect samples for urinalysis	x						
Perform complete physical examination with neurologic examination (see Appendix C) and visual acuity examination (Snellen or equivalent)	x				x		
Collect resting vital signs, including temperature <sup>b</sup>	x <sup>c</sup>	x	x	x	x	x	x <sup>d</sup>
Perform 12-lead ECG	x						
Solicit subject-reported pain using Wong-Baker faces pain rating scale (see Appendix D)	x		x	x	x		
Blinded investigator to record lesion measurement and assessment of signs and symptoms of cSSTI (see Appendix A and Appendix E)	x		x	x	x	x	
Record AE- or cSSTI-related <sup>e</sup> procedures	x		x	x	x	x	x
Collect sample for CBC with differential and serum chemistry panel (see Appendix F)	x			x	x	x	x <sup>d</sup>
Collect serum sample for pregnancy test, females of childbearing potential only. Urine test may be used locally at screening provided the local test is one with high sensitivity (ie, has the ability to detect 10 mIU/mL hCG) <sup>f</sup>	x				x		
Collect blood for culture (see Appendix B) <sup>g</sup>	x		x	x	x	x	x <sup>h</sup>

<b>Study Procedures</b>	<b>Screening</b> (Day -1 or Day 1; day of infusion or previous calendar day)	<b>Day 1</b>	<b>48-72 Hours</b>	<b>Day 7 (+2)</b>	<b>EOT (Day 11+2)</b>	<b>TOC</b> (18 to 25 days after start of first infusion)	<b>Late Follow- Up<sup>a</sup></b> (32 to 39 days after start of first infusion)
Obtain cSSTI site specimen (see Appendix B)	x		x <sup>i</sup>	x <sup>i</sup>	x <sup>i</sup>	x <sup>i</sup>	x <sup>h,i</sup>
Record prior or concomitant medications <sup>j</sup>	x	x	x	x	x	x	x
Assess AEs <sup>k</sup>	x	x	x	x	x	x	x
Randomize via interactive voice response system		x					
Collect sample for PK analysis (see Appendix G)		x	x	x			
Administer IV or oral study drug <sup>l</sup>		x	x	x			
Assess for possible switch to oral <sup>m</sup>			x	x			
Assess palatability of tedizolid phosphate oral tablets <sup>n</sup> (see Appendix H)			x				
Instruct subject on study drug administration procedure, dispense study drug and diary, if appropriate <sup>o</sup>		x	x	x			
Record information from diary and returned packaging <sup>o</sup>			x	x	x		
Perform directed physical examination with neurologic examination (see Appendix C)			x	x		x	x <sup>d</sup>
Perform Blinded Investigator's assessment of clinical response (see Table 5)					x	x	
Assess clinical relapse by Blinded Investigator (only if success at TOC Visit)							x
Abbreviations: AE=adverse event; CBC=complete blood count; e-CRF=electronic case report form; cSSTI=complicated skin and soft tissue infection; ECG=electrocardiogram; EOT=end of therapy; IV=intravenous; PK=pharmacokinetic; TOC=Test of Cure; SAE=serious adverse event. Note: day refers to calendar day, not a 24-hour time period.							

*Footnotes for TR701-122/MK-1986-012 Study Assessments*

- a A telephone interview is acceptable for subjects who do not have symptoms of clinical relapse, ongoing AEs, new or ongoing SAEs, or laboratory abnormalities that require an on-site follow-up visit with a healthcare provider. If telephone interview: record questions and responses.
- b Perform prior to start of study drug infusion.
- c If multiple temperature measurements are obtained and recorded in the source document at the Screening Visit, record the highest measurement in the eCRF.
- d Performed if on-site visit only.
- e Eg, puncture, debridement, and incision and drainage. When clinically indicated, use imaging techniques to rule out osteomyelitis for deep wound infections in proximity to bone or joints.
- f At the Screening Visit, a local laboratory serum or high sensitivity urine (ie, capable of detecting 10 mIU/mL) test is acceptable for enrollment; send an additional serum sample to the central laboratory. At EOT, a central laboratory serum test is required.
- g Collect 1 sample for aerobic and 1 for anaerobic culture; blood cultures for anaerobic pathogens are required only at sites where it is a local standard of care. Repeat blood cultures after baseline only if previously positive or as clinically indicated.
- h Performed at on-site visit only for subjects not categorized as a failure at a prior visit, or if clinically indicated.
- i Perform after Day 1 only if clinically indicated. Appropriate cSSTI site specimens (superficial swab not acceptable) at baseline will be evaluated with Gram stain and by culture and susceptibility testing. Culture for anaerobes should be performed at sites where this is a standard of care. After baseline, cSSTI site specimens are only required in subjects with no improvement or with deterioration of the primary lesion, and if the lesion is easily accessible. Obtain a specimen on Day 1 only if the Screening Visit sample was inadequate or is not available for testing.
- j Record medications used within 30 days before the first infusion of study drug through the Late Follow-Up Visit.
- k The AE reporting period is after signing informed consent form through 30 days after the last study drug administration. Follow SAEs until stabilization, resolution/death, or consent is withdrawn.
- l Subjects will receive IV and/or oral tedizolid phosphate for 6 consecutive days of treatment or IV and/or oral Comparator for 10 consecutive days of treatment. While subject is receiving IV therapy, flush IV line before and after study drug administration. No other IV therapy should be administered concurrent with the study drug. Monitor the subject for at least 30 minutes postinfusion for AEs.
- m If switch to oral treatment is assessed at an unscheduled visit, obtain vital signs and lesion measurements. Call the interactive voice response system when switching to oral treatment.
- n Assess palatability of tedizolid phosphate tablets **one time only** after first oral administration
- o At the Investigator's discretion, oral study drug can be dispensed with a diary to document date and time of study drug self-administration. Subjects are to return remaining drug packaging and the diary to the study site at the 48-72 Hour, Day 7, and EOT Visits, as applicable. The diary should be signed/dated by the individual who enters the data and the site staff who receives the data and reviews it with the subject or guardian.

## 6.2 Number of Subjects

At least 120 subjects are to be enrolled (randomized) with at least 86 receiving tedizolid phosphate and evaluable for the safety analysis.

## 6.3 Treatment Assignment

After the subject has signed the informed consent form (ICF)/assent form and study eligibility is confirmed, the study site designee or other study personnel will obtain the subject's study number and study drug assignment from a computer-generated randomization code via an interactive voice response system (IVRS) or interactive web response system (IWRS). The subject is considered randomized when the IVRS/IWRS provides the study number and study drug assignment (tedizolid phosphate or Comparator), regardless of whether the subject actually receives any study drug.

## 7.0 SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects will be categorized into 1 of 3 clinical syndromes: cellulitis/erysipelas, major cutaneous abscess, and wound infection.

### 7.1 Subject Inclusion Criteria

Subjects who meet all of the following criteria are eligible for the study:

1. Males or females 12 years to <18 years
2. Adequate venous access for IV administration of study drug for at least 24 hours (for those subjects receiving IV study medication) and for collection of protocol-specified blood samples
3. Local symptoms must have started within 7 days before Study Day -1
4. Subjects that failed prior therapy for the primary infection site (no improvement in signs and symptoms [eg, fever, pain, tenderness, lesion size increasing] after at least 2 full days of antimicrobial therapy) are permitted in the study
5. cSSTI meeting at least 1 of the following clinical syndrome definitions:
  - a. **Cellulitis/erysipelas defined as a diffuse skin infection, characterized by all of the following:**
    - Spreading area of erythema, edema, and/or induration (EEI) extending at least 4 cm in 1 dimension
    - No collection of pus apparent upon visual examination (diagnosis still consistent with cellulitis/erysipelas if pus is collected from the lesion)

- At least 2 of the following signs of infection:
  - Erythema
  - Induration
  - Swelling/edema
  - Localized warmth
  - Pain or tenderness
- At least one of the following signs of severe infection:
  - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
  - Presence of lymphangitis
  - Fever, defined as body temperature  $\geq 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) oral or  $\geq 38.4^{\circ}\text{C}$  ( $101.1^{\circ}\text{F}$ ) tympanic or rectal (observed by a health care provider)
  - WBC count  $\geq 10,000$  cells/mm<sup>3</sup> or  $< 4000$  cells/mm<sup>3</sup>
  - $> 10\%$  immature neutrophils
  - Patient-reported pain of at least 6 (Wong-Baker pain scale)
- b. **Major cutaneous abscess, defined as an infection characterized by a collection of pus suggested by physical examination that is intradermal or deeper and is accompanied by the following:**
  - Erythema, edema and or induration (EEI) extending at least 4 cm in 1 dimension.
  - At least 2 of the following signs of infection:
    - Erythema
    - Induration
    - Swelling/Edema
    - Localized Warmth
    - Pain or Tenderness
    - Fluctuance
    - Incision and drainage considered or performed
    - Seropurulent Drainage
    - Intradermal or subcutaneous fluid collection visualized by ultrasonography or other radiologic study

- At least one of the following signs of severe infection:
  - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
  - Presence of lymphangitis
  - Fever, defined as body temperature  $\geq 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) oral or  $\geq 38.4^{\circ}\text{C}$  ( $101.1^{\circ}\text{F}$ ) tympanic or rectal (observed by a health care provider)
  - WBC count  $\geq 10,000$  cells/mm<sup>3</sup> or  $< 4000$  cells/mm<sup>3</sup>
  - $> 10\%$  immature neutrophils
  - Patient-reported pain of at least 6 (Wong-Baker pain scale)
- c. **Wound infection, defined as an infection characterized by purulent drainage from a wound with surrounding EEI, and further defined by the following:**
- Superficial incision surgical site infection (SSI) meeting all of the following criteria:
  - Follows clean surgery (elective, not emergency, nontraumatic, primarily closed, no acute inflammation; no break in technique; respiratory, gastrointestinal, biliary, and genitourinary tracts not entered).
  - Involves only the skin or subcutaneous tissue around the incision, does not involve fascia.
  - Occurs within 30 days after procedure
  - Original surgical incision  $\geq 1$  cm
  - Purulent drainage (spontaneous or therapeutic) with surrounding EEI extending at least 4 cm in 1 dimension
- Or, post-traumatic wound (including penetrating trauma) characterized by purulent drainage (spontaneous or therapeutic) with surrounding EEI extending at least 4 cm in 1 dimension
- At least one of the following signs of severe infection:
  - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
  - Presence of lymphangitis
  - Fever, defined as body temperature  $\geq 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) oral or  $\geq 38.4^{\circ}\text{C}$  ( $101.1^{\circ}\text{F}$ ) tympanic or rectal (observed by a health care provider)

- WBC count  $\geq 10,000$  cells/mm<sup>3</sup> or  $< 4000$  cells/mm<sup>3</sup>
  - $> 10\%$  immature neutrophils
  - Patient-reported pain of at least 6 (Wong-Baker pain scale)
6. Suspected or documented gram-positive infection from baseline Gram stain or culture (see Appendix B). The microbiological sample must have been collected using a valid sampling technique, such as an aspirate, biopsy, incision, deep swab, etc. A superficial swab is not acceptable. Specimens for culture are required for abscesses and wounds at the Screening Visit; specimens for cellulitis are to be collected according to standard practice at the site.
  7. Parent/LAR able to give informed consent and willing and able to comply with all required study procedures. Assent is also required of children who, in the investigator's judgment, are capable of understanding the nature of the study.

## 7.2 Subject Exclusion Criteria

Subjects who meet any of the following criteria are not eligible to participate in this study:

1. Uncomplicated minor skin and skin structure infections such as pustules, folliculitis, furuncles, minor abscesses (small volume of suppuration not surrounded by cellulitis/erysipelas), impetiginous lesions, superficial or limited cellulitis/erysipelas, and minor wound-associated foreign body reactions (eg, "stitch abscesses")
2. cSSTI due to or associated with any of the following:
  - Suspected or documented infection caused by gram-negative pathogens in subjects with cellulitis/erysipelas or major cutaneous abscess that requires an antibiotic with specific gram-negative coverage. Subjects with wound infections where gram-negative adjunctive therapy is warranted may be enrolled if they meet the other eligibility criteria.
  - Perianal abscess
  - cSSTI within the mouth and/or perioral structures or within the hairline (if this is limits measurements of lesion size)
  - Infections associated with, or in close proximity to, a prosthetic device
  - Concomitant severe acute bacterial infection at another site not including a secondary cSSTI lesion (eg, septic arthritis, endocarditis, osteomyelitis)
  - Infected burns
  - Any rapidly evolving necrotizing process involving deep soft tissue structures (ie, necrotizing fasciitis, pyomyositis)
  - Infected human or animal bites
  - Infections at vascular catheter sites or involving thrombophlebitis

- Incision SSI with any of the following characteristics:
    - Follows clean-contaminated surgery (urgent or emergency case that is otherwise clean, elective opening of respiratory, gastrointestinal, biliary, or genitourinary tract with minimal spillage [eg, appendectomy] not encountering infected urine or bile; minor technique break)
    - Follows contaminated surgery (nonpurulent inflammation; gross spillage from gastrointestinal tract; entry into biliary or genitourinary tract in the presence of infected bile or urine; major break in technique; chronic open wounds to be grafted or covered)
    - Follows surgery in a contaminated location (purulent inflammation [eg, abscess]; preoperative perforation of respiratory, gastrointestinal, biliary, or genitourinary tract)
    - Extends into the fascia or muscle layers, organs, or spaces
  - 3. Known bacteremia at the Screening Visit, severe sepsis or septic shock
  - 4. Recent history of opportunistic infections where the underlying cause of these infections is still active (eg, leukemia, transplant, acquired immunodeficiency syndrome)
  - 5. Receiving treatment for active tuberculosis
  - 6. Known or suspected severe neutropenia (absolute neutrophil count  $<500$  cells/mm<sup>3</sup>)
  - 7. Human immunodeficiency virus positive and CD4 cell counts  $<200$  cells/mm<sup>3</sup> (known or suspected)
  - 8. Renal impairment requiring peritoneal dialysis, plasmapheresis, hemodialysis, venovenous dialysis, or other forms of renal filtration
  - 9. Known or suspected severe hepatic impairment
  - 10. Cardiac or ECG finding which in the opinion of the Investigator would limit the subject's ability to complete and/or participate in this clinical study
  - 11. Received more than 24 hours of effective antibacterial drug therapy for treatment of the current episode of cSSTI; prior therapy must be short acting (administration frequency is 1 or more doses per 24 hours)
  - 12. Topical antibacterial ointments or creams applied to and remaining on the primary lesion prior to randomization for a duration of  $\geq 24$  hours, except for antibiotic/antiseptic-coated dressings applied to clean postsurgical wounds
- Note:** As with systemic antibacterial therapy, longer durations of topical treatments without apparent effectiveness (see Inclusion Criterion #4: at least 2 full days of treatment without improvement in signs and symptoms) are permitted.

13. Treatment with investigational medicinal product within 30 days before the first infusion of study drug
14. Investigational device present or removed <30 days before the first infusion of study drug or presence of device-related infection
15. Previous inclusion in the tedizolid phosphate development program
16. Hypersensitivity to tedizolid phosphate or any component in the formulation
17. Hypersensitivity to all of the comparator drugs; hypersensitivity to a comparator drug does not preclude participation if an alternative comparator can be used
18. For subjects with wound infections: history of hypersensitivity to ceftazidime, aztreonam, or any component of the aztreonam formulation, if aztreonam adjunctive therapy is required; history of hypersensitivity to metronidazole or any component of the formulation, if metronidazole adjunctive therapy is required
19. Female subjects who are pregnant or nursing, or who are of childbearing potential and unwilling to use an acceptable method of birth control (eg, abstinence, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel]), or male partner sterilization
20. Subjects and/or LAR who the Investigator considers unlikely to adhere to the protocol, comply with study drug administration, or complete the clinical study
21. Significant or life-threatening condition or organ or system condition or disease (eg, endocarditis, meningitis)
22. Need for oral administration of methotrexate, topotecan, irinotecan or rosuvastatin, during administration of oral study drug  
**Note:** Administration of these concomitant medications during the follow-up period is allowed, as is administration during treatment with *intravenous* tedizolid phosphate.
23. Use of monoamine oxidase inhibitors, tricyclic antidepressants, buspirone, selective serotonin reuptake inhibitors and serotonin 5 hydroxytryptamine receptor agonists (triptans) within 14 days prior to study drug administration

### **7.3 Subject Withdrawal Criteria**

#### **7.3.1 Subject Withdrawal From the Study**

Subjects may withdraw or be withdrawn from the study at any time. Subjects may be withdrawn from the study at the request of the Investigator or Sponsor. Reasonable efforts are to be made to complete all protocol-specified assessments listed for the EOT Visit at the time of withdrawal and to perform follow-up safety assessments. Complete the safety assessments for the EOT Visit before beginning new antibiotic therapy. Subjects who withdraw or are withdrawn will not be replaced.

### 7.3.2 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

Subjects may discontinue treatment at any time, for any reason, or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate; the trial plan is violated, for administrative and/or other safety reasons.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the reasons described below.

For subjects with major cutaneous abscess or cellulitis/erysipelas, adjunctive antibacterial therapy is prohibited and subjects determined to have a gram-negative pathogen causing the cSSTI are excluded from enrollment. Subjects randomized before culture results are available and later determined to have a gram-negative pathogen that requires antibiotic therapy will discontinue study drug and complete assessments for safety.

For subjects with wound infection:

- In countries where aztreonam is available, adjunctive aztreonam (IV) and/or metronidazole (IV or oral) may be initiated on Day 1 or during the first 3 days of treatment if the subject is determined or suspected to have a gram-negative aerobic or anaerobic pathogen, respectively, causing the cSSTI. Subjects later determined to have an infection caused by a gram-negative pathogen, but no gram-positive pathogen, will discontinue study drug and complete assessments for safety.
- In countries where IV aztreonam is not available, subjects should not be enrolled if they are known or suspected to have an infection caused by a gram-negative pathogen that will require treatment.

Other reasons for discontinuation of study drug include, but are not limited to, the following:

- Subject or LAR requests discontinuation of the study drug or withdrawal from the study
- Unacceptable toxicity, including but not limited to clinically relevant hematological changes suggesting myelosuppression, evidence of new or worsening hepatic dysfunction, *C. difficile*-associated diarrhea, evidence of optic or peripheral neuropathy, lactic acidosis, or serotonin syndrome
- Subject becomes pregnant
- Investigator-assessed treatment failure (subject should receive rescue therapy following Investigator's judgment) Investigator considers a change of therapy would be in the best interest of the subject

In most cases, all study procedures and assessments should be conducted (other than study drug administration, IV to oral switch assessment, PK sample collection, and study drug palatability) even if the subject is discontinued early from treatment, as per [Table 3](#).

Exceptions are as follows:

- Removal of consent/assent: no further assessments are conducted.
- Presence of gram negative pathogen requiring treatment which, for scenarios outlined previously in this Section, requires discontinuation of study medication and initiation of rescue medication: only safety assessments (clinical labs, physical exams/vital sign measurements, neurological exams, visual acuity exams, adverse events, concomitant medications) need to be conducted. Efficacy assessments (such as lesion size measurements and clinical response and relapse assessments) should be skipped.

### **7.3.3 Study Discontinuation**

Sponsor reserves the option to terminate the study at any time. Reasons for terminating the study or terminating the participation of a specific site include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies with the study drug indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording are inaccurate or incomplete
- The Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study
- The IRB/EC/REB decides to terminate or suspend approval for the study or the Investigator
- The Investigator asks to withdraw from study participation

## **8.0 TREATMENT OF SUBJECTS**

### **8.1 Description of Study Drug**

The investigational study drug is tedizolid phosphate, also known by the investigational numbers TR701-FA and MK-1986, given intravenously and/or orally for total of 6 days. Comparator study drugs are given intravenously and/or orally for a total of 10 days and are provided by the site for administration, with dose determined by local clinical practice. At least 50% of subjects will receive all study drug administrations required for a minimum 24-hour period of IV therapy before the Investigator assesses for a switch to oral therapy.

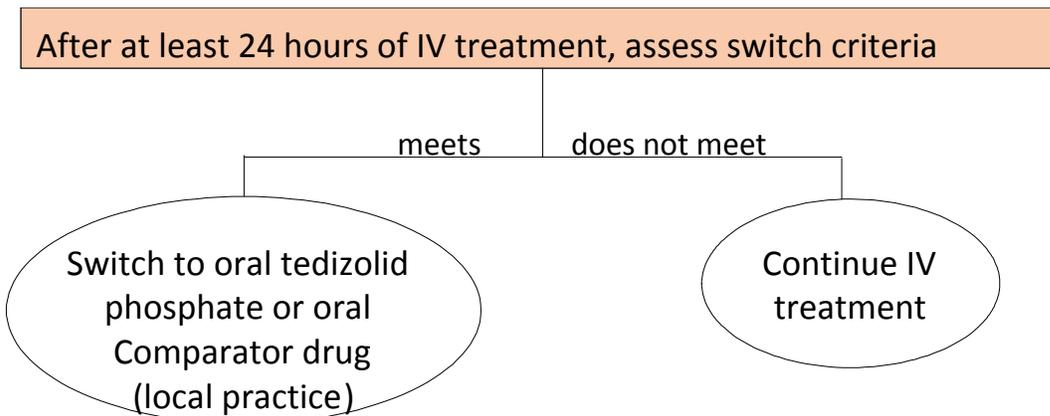
## 8.2 Assessment for IV to Oral Switch

While subjects may receive IV therapy for the entire treatment duration, the optional switch to oral therapy may occur when the following criteria are met:

- The primary skin lesion size has not increased from baseline in length or width
- Last temperature is  $<37.7^{\circ}\text{C}$
- Signs or symptoms of the primary cSSTI site have not worsened and at least 1 has improved from baseline

A schema describing the assessment for IV to oral switch is shown in [Figure 2](#).

Figure 2: Assessment for IV to Oral Switch



Abbreviations: IV=intravenous

## 8.3 Concomitant Medications

Prior and concomitant therapies are to be recorded as follows:

- All concomitant medications used within 30 days before the first infusion of study drug through the Late Follow-up (LFU) Visit
- Surgical procedures such as incision and drainage, debridement, aspiration puncture, or excision with or without grafting used to treat the primary lesion of cSSTI within 2 days before the first infusion of study drug through the LFU Visit. Detailed information on the need for additional surgical procedures is required to ensure appropriate clinical response categorization to differentiate drug failure from inadequate surgical procedure or for diagnostic purposes

- Chlorhexidine or other disinfectant applications for decontamination (body wash, topical antibiotics, nasal decontamination, etc.) used within 24 hours before the first infusion of study drug through the LFU Visit
- All procedures to treat an adverse event

A list of prohibited and allowed therapies and subject restrictions is provided in [Table 4](#).

Table 4: Concomitant Therapy Rules

Category	Medications and Procedures	Comments on Use <sup>a</sup>
<b>Allowed</b>	Adjunctive aztreonam and/or metronidazole in subjects with wound infection	When gram-negative pathogens are suspected or confirmed
	Supportive measures for optimal medical care (such as debridement, wound packing, wound lavage, aspiration puncture, excision with or without grafting, etc.)	As needed throughout study; detailed information is required to ensure appropriate clinical response categorization
<b>Prohibited</b>	Concomitant systemic antibiotics (except adjunctive aztreonam and/or metronidazole in subjects with wound infections). If therapy is required to treat an infection other than that associated with the primary cSSTI, such antibiotic therapy should not have overlapping antibacterial activity with the study drug for the pathogen isolated from the cSSTI lesion at baseline, if possible	Prohibited 24 hours prior to the start of the first dose through the LFU Visit; prior therapy must be short acting (administration frequency is 1 or more doses per 24 hours). Antibiotics without activity against cSSTI pathogens or those with local activity are allowed
	Topical antibacterial ointments or creams applied to and remaining on the primary lesion <b>prior to randomization for a duration of ≥24 hours</b> , except for antibiotic/antiseptic-coated dressings applied to clean postsurgical wounds  <b>Note:</b> As with systemic antibacterial therapy, longer durations of topical treatments <i>without</i> apparent effectiveness (see Inclusion Criterion #4: at least 2 full days of treatment without improvement in signs and symptoms) are permitted.	Prohibited 24 hours prior to the start of the first infusion through the LFU Visit; topical antibiotic outside the primary lesion is allowed
	Monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin 5-hydroxytryptamine receptor agonists (triptans) and buspirone	Refer to Appendix I for examples. Prohibited from 14 days prior to study through the EOT visit

Abbreviations: cSSTI=complicated skin and skin tissue infection; LFU=late follow-up.

<sup>a</sup> Please refer to Section 7.2 for details on exclusion criteria

#### **8.4 Treatment Compliance**

No measurements of treatment compliance are planned.

The infusion date and start and stop times will be recorded in the source documents and electronic case report form (e-CRF). In the event of a missed dose, please contact Sponsor or designee to discuss how to continue therapy.

If study drug is administered at home, subjects are to keep a diary of the date and time the study drug was taken. The study drug diary and used study drug packaging, if applicable, are to be returned to study site personnel at the next scheduled study visit. Study site personnel will review the study diary, examine the study drug, and document their findings on the appropriate e-CRF.

#### **8.5 Randomization and Blinding**

Subjects will be randomized 3:1 tedizolid phosphate: comparator using an IVRS/IWRS with randomization stratified by geographic region. Sponsor designee (eg, IVRS/IWRS vendor) will maintain the randomization codes in accordance with standard operating procedures to ensure the blind is properly maintained. The efficacy evaluator and the evaluator of AE relationship (i.e. Blinded Investigator) are blinded to study treatment.

### **9.0 STUDY DRUG MATERIALS AND MANAGEMENT**

#### **9.1 Study Drug**

The investigational study drug is tedizolid phosphate, also known as MK-1986 and TR-701 FA.

##### *Intravenous Form*

Tedizolid Phosphate is formulated as a sterile lyophilized powder for injection for IV administration. Tedizolid Phosphate for Injection, 200 mg/vial, consists of Tedizolid Phosphate, mannitol, and sodium hydroxide that are lyophilized in a 10 mL clear glass vial with a 20 mm gray chlorobutyl rubber stopper and a 20 mm flip-off seal. The resulting drug product is a white to off-white cake that results in a clear light-yellow solution after reconstitution.

Tedizolid Phosphate for Injection, 200 mg/vial will be manufactured according to Good Manufacturing Practice (GMP) requirements. Additional information is provided in the Pharmacy Manual.

##### *Oral Form*

Tedizolid Phosphate is formulated as an immediate-release film-coated tablet for oral administration. Tedizolid Phosphate Tablets, 200 mg, consists of Tedizolid Phosphate, microcrystalline cellulose, mannitol, povidone, crospovidone, and magnesium stearate, which are compressed into a modified oval tablet with an Opadry II Yellow-film coat.

Tedizolid Phosphate Tablets, 200 mg will be manufactured according to GMP requirements. A complete list of ingredients is provided in the Pharmacy Manual.

Comparator study drugs are provided by the site for both IV and oral administration, with selection and dose determined by local clinical practice. For sites that are not permitted by local regulation or are otherwise unable to supply the Comparators, Sponsor will arrange the supply of the appropriate comparator drugs. The IV Comparators are vancomycin, linezolid, clindamycin, flucloxacillin, and cefazolin. The oral Comparators are linezolid, clindamycin, flucloxacillin, and cephalexin. (Note: Linezolid is allowed as a comparator outside of Europe only.)

Aztreonam and metronidazole will be supplied by the site. **Aztreonam and metronidazole must be available at the site prior to the site's enrollment of any subject with wound infection with a suspected or known gram-negative pathogen.**

Use as directed in the package insert. Intravenous administration of metronidazole is acceptable.

## 9.2 Study Drug Packaging and Labeling

Tedizolid Phosphate Tablets, 200 mg, will be packaged as an open label in 6-tablet bottles.

A lyophilized vial of 200 mg (50 mg/mL) Tedizolid Phosphate for Injection, 200 mg/vial will be packaged as an open label in 20-vial kits. Tedizolid Phosphate for Injection, 200 mg/vial will be prepared by qualified clinical staff following directions provided in the Pharmacy Manual.

## 9.3 Study Drug Storage

Store all study medication at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) under secure conditions. Store aztreonam, metronidazole, and all comparators according to the instructions in their respective package inserts. Subjects will be instructed to store oral study medication as follows:

- Keep away from excessive heat, light, and humidity
- Keep tablets in the bottle until ready to take them
- Do not store in refrigerator or freezer
- Do not leave in a hot car
- Do not leave in a hot or humid bathroom

## 9.4 Study Drug Preparation

A lyophilized vial of 200 mg (50 mg/mL) Tedizolid Phosphate for Injection, 200 mg/vial will be prepared by qualified clinical staff. The vial should be reconstituted with 4 mL of Sterile Water for Injection and 4 mL of the reconstituted solution should be withdrawn from the vial and added to an IV bag containing 0.9% Sodium Chloride Injection, for IV administration for a total volume of 250 mL. Additional information is provided in the Pharmacy Manual.

## 9.5 Administration

Oral tedizolid phosphate may be taken with or without food; follow the label instructions for administration of oral comparator. It is recommended to deliver the IV tedizolid phosphate using a 22 gauge catheter, preferably inserted on the back of the hand or wrist. It is recommended to cover the venous catheter with transparent adhesive with no gauze and monitor the site regularly. Flush IV line before and after study drug administration, per standard of care. No other IV therapy should be administered concurrently with the study drug.

All subjects assigned to IV study drug must receive the first 24-hours of IV study treatment in a healthcare setting but, at the Investigator's discretion, subjects are allowed to take the oral study drug at home. A switch to oral administration may be considered following the criteria in Section 8.2.

For IV treatment, the entire contents of the infusion bag will be administered and the subject will be monitored for at least 30 minutes postinfusion. All tedizolid phosphate infusions will be 60±10 minutes and start and stop time will be recorded in the source documents and e-CRFs. For administration of the Comparator study drug, follow the package insert for the specific drug.

### Adjunctive Aztreonam and/or Metronidazole Therapy

For subjects with wound infections only, aztreonam and/or metronidazole can be added for known or suspected gram-negative aerobic or anaerobic pathogens, respectively. Aztreonam and metronidazole must be available at the site prior to the site's enrollment of any subject with wound infection with a known or suspected gram-negative pathogen. Aztreonam and/or metronidazole therapy may be initiated on Day 1 or during the first 3 days of treatment if a gram-negative pathogen is suspected or confirmed (eg, Gram stain at the site, local laboratory, or other local institution where the subject was first diagnosed). Administer aztreonam (IV) and/or metronidazole (IV or oral) as directed in the package insert. If given IV, do not administer concurrent with the study drug. Flush line between administrations. When aztreonam and/or metronidazole therapy is appropriate, it is to be prescribed for a maximum of 10 days, but discontinued no later than the EOT Visit.

In countries and/or sites where IV aztreonam is not available, subjects with wound infections should not be enrolled if they are known or suspected to have a gram-negative pathogen that will require treatment (see also Section 7.3.2).

## 9.6 Study Drug Accountability

All tedizolid phosphate required for completion of this study will be provided by Sponsor or Sponsor's designee. The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced. Accurate records of all study drug dispensed from and returned to the study site are to be maintained. A Study Monitor will be responsible for checking drug accountability at the study site. Inventory records must be available for inspection by Sponsor, a designee of Sponsor, or an authorized Health Authority inspector at any time. The Investigator will be responsible for ensuring the study drug is used in accordance with this protocol.

Additional information is provided in the Pharmacy Manual.

### **9.7 Study Drug Handling and Disposal**

All unused study drug tablets, IV materials, and unused and used packaging are to be retained at the study site until receipt of written instruction from Sponsor regarding disposition. All records related to study drug supply and disposition are to be maintained by the study site.

### **10.0 ASSESSMENT OF EFFICACY**

The timing of efficacy assessments is provided in [Table 3](#). All efficacy assessments are to be performed by an investigator who is blinded to treatment.

#### **10.1 Assessment of Efficacy Variables**

The primary efficacy outcome is the Blinded Investigator's assessment of clinical success at the TOC Visit in the ITT and CE-TOC Analysis Sets. A subject assessed as a clinical failure at any time during the study is considered a clinical failure at the TOC Visit.

Secondary efficacy outcomes are the following:

- Programmatic determination of early clinical response at the 48-72 Hour Visit in the ITT Analysis Set. A response of success is  $\geq 20\%$  reduction from baseline lesion area (defined as length x width of the EEI); a response of success would categorize the subject as a responder. A response of failure is a  $< 20\%$  reduction in lesion area; a response of failure would categorize the subject as a none responder
- Blinded Investigator's assessment of clinical success at the EOT Visit in the ITT and CE-EOT Analysis Sets

Additional efficacy outcomes are the following:

- Change from baseline in lesion size, assessment of signs and symptoms, and regional or systemic signs (lymphadenopathy, temperature, percentage immature neutrophils, WBC count)
- Per-pathogen microbiological response at the TOC Visit in the MITT and ME Analysis Sets
- Per-subject microbiological response at the TOC Visit in the MITT and ME Analysis Sets
- Blinded Investigator's assessment of clinical success at the TOC Visit in the MITT and ME Analysis Sets
- Per-pathogen Blinded Investigator's assessment of clinical success at the TOC Visit in the MITT and ME Analysis Sets
- Subject-Reported Outcome assessment (pain)

## **10.2 Response Definitions**

### **10.2.1 Clinical Response Definitions**

The primary efficacy outcome is the Blinded Investigator's assessment of clinical success at the TOC Visit. A subject assessed as a clinical failure at any time during the study is considered a clinical failure at the TOC Visit.

Response definitions for the Blinded Investigator's assessment and the programmatic assessment are provided in [Table 5](#) and [Table 6](#), and Blinded Investigator's assessment of clinical relapse in [Table 7](#). The clinical response assessment may be performed by a physician or qualified delegate, such as a nurse practitioner or physician's assistant.

Table 5: Blinded Investigator’s Assessment of Clinical Response Definitions (EOT, TOC Visits)

Term	Definition
<b>Clinical Success</b>	All of the following: <ul style="list-style-type: none"> <li>• Resolution or near resolution of most disease-specific signs and symptoms</li> <li>• Absence or near resolution of regional or systemic signs of infection (lymphadenopathy, fever, &gt;10% immature neutrophils, abnormal white blood cell count), if present at baseline</li> <li>• No new signs, symptoms, or complications attributable to the infection under study so no further antibiotic therapy is required for the treatment of the primary lesion</li> </ul>
<b>Clinical Failure</b>	Any of the following: <ul style="list-style-type: none"> <li>• Requires additional antibiotic therapy for treatment of the primary lesion</li> <li>• Unplanned major surgical intervention required due to failure of study drug (ie, amputation)</li> <li>• Developed osteomyelitis after baseline</li> <li>• Persistent gram-positive pathogen bacteremia</li> <li>• Treatment-emergent adverse event leading to discontinuation of study drug and subject required additional antibiotic therapy to treat the infection under study</li> <li>• Death (all-cause mortality) within 28 days of first infusion</li> </ul>
<b>Indeterminate</b>	Study data are not available for the evaluation of efficacy for any reason including: <ul style="list-style-type: none"> <li>• Osteomyelitis present at baseline</li> <li>• Subject lost to follow-up</li> <li>• Extenuating circumstances that preclude the classification of a clinical success or failure</li> <li>• For subjects with cellulitis/erysipelas or major cutaneous abscess: gram-negative pathogen isolated at baseline that required a different antibiotic therapy</li> <li>• For subjects with wound infections: gram-negative pathogen isolated at baseline that required a different antibiotic therapy other than aztreonam or metronidazole</li> <li>• Subject withdraws consent</li> </ul>

Note: The clinical response assessment may be performed by a physician or qualified delegate, such as a nurse practitioner or physician’s assistant.

Table 6: Programmatic Assessment of Clinical Response Definitions (48-72 Hour Visit)

Term	Definition
<b>Success/Responder</b>	≥20% reduction from baseline lesion area
<b>Failure/Nonresponder</b>	<20% reduction from baseline lesion area
<b>Indeterminate</b>	Lesion area data missing

Table 7: Blinded Investigator’s Assessment of Clinical Relapse Definitions (Late Follow-up Visit)

Term	Definition
<b>Sustained Clinical Success</b>	No new signs or symptoms of primary cSSTI after TOC
<b>Relapse</b>	New or worsened signs or symptoms of primary cSSTI after TOC
<b>Indeterminate</b>	Study data are not available for the evaluation of efficacy for any reason including the following: <ul style="list-style-type: none"> <li>• Subject lost to follow-up</li> <li>• Extenuating circumstances that preclude the classification of a clinical success or relapse</li> <li>• Subject withdraws consent</li> </ul>

Abbreviations: cSSTI=complicated skin and soft tissue infection; TOC=test of cure visit.  
 Note: If LFU Visit occurs via telephone contact, assessment may be based on the subject’s report.

### 10.2.2 Microbiological Response Definitions

Microbiological response definitions are as presented in [Table 8](#) and [Table 9](#). Note that microbiological samples are required at baseline, but after baseline, are only required in subjects with no improvement or with deterioration of the primary lesion, and if the lesion is easily accessible. Subjects with an unfavorable microbiological response (persistence or presumed persistence) at the EOT Visit will be assigned an unfavorable microbiological response at TOC. Microbiological response will be determined based on the data from the central microbiology laboratory and the Blinded Investigator’s assessment of clinical response.

Table 8: Microbiological Response Definitions

<b>Term</b>	<b>Definition</b>
<b>Eradication</b>	Absence of original baseline pathogen(s)
<b>Presumed Eradication</b>	No source specimen to culture in a subject assessed as a clinical success by the Investigator
<b>Persistence</b>	Continued presence of the original baseline pathogen(s)
<b>Presumed Persistence</b>	No source specimen to culture in a subject assessed as a clinical failure by the Investigator
<b>Recurrence</b>	Identification of original baseline pathogen(s) after clearance
<b>Indeterminate</b>	The subject's clinical response is indeterminate or other circumstance that precludes a microbiological evaluation

Note: Response is per pathogen and the per subject outcome is based on all pathogens present at baseline

Table 9: Microbiological Response Definitions: Superinfection or New Infection

Superinfection	Isolation of a nonbaseline pathogen from the primary cSSTI site (excluding superficial swabs) while the subject is receiving study drug and the subject has worsening or new signs or symptoms of the primary cSSTI
New infection	Isolation of a nonbaseline pathogen from a post-treatment culture from the primary cSSTI site (excluding superficial swabs) in a subject with worsening or new signs or symptoms of the primary cSSTI

Abbreviations: cSSTI=complicated skin and soft tissue infection.

### 10.3 Evaluability Review Team

The Evaluability Review Team (ERT) is to review both clinical and microbiological data to determine whether subjects meet the criteria for inclusion in the analysis sets and for determination of baseline and post baseline pathogens. The ERT is to consist of a Sponsor medical representative and a clinical operations representative at a minimum. The ERT members are to be blinded to treatment assignment and are to review the data concurrent with the conduct of the study. The ERT will be conducted in accordance with the Blinding, Evaluability, and Microbiological Assessment Plan.

### 10.4 Sample Collection for Microbiology Assessment

Collect samples at time points defined in [Table 3](#). Microbiological specimens are to be sent to the local laboratory and, for subjects who are randomized, also send samples to the central laboratory, as shown in [Table 10](#). Specimens for culture are required for abscesses and wounds at screening; cellulitis specimens are to be collected according to standard practice at the site.

Table 10: Samples for Microbiology Assessments

Sample	Laboratory		Comments <sup>b</sup>
	Local	Central <sup>a</sup>	
<b>Appropriate cSSTI site specimen</b>			All samples collected for microbiological assessment must be collected via valid sampling technique (aspirate, biopsy, deep swab, etc.; superficial swab not acceptable)
Gram stain and culture	×		Culture for aerobes and anaerobes <sup>c</sup>
Isolates from local laboratory culture for confirmation of identification and susceptibility testing		×	Send all isolates from the local laboratory culture to the central laboratory except for those listed as never a pathogen in Appendix B
<b>Blood Cultures</b>			Collect 1 vial for aerobic testing and 1 for anaerobic testing (for a total of 2 vials) <sup>c</sup>
Gram stain (optional) and culture	×		Send both vials to same local laboratory
Isolates from blood culture for confirmation of identification and susceptibility testing		×	Send all isolates from a local laboratory culture to the central laboratory If blood culture is positive, repeat within 24 hours

<sup>a</sup> The study site is to send samples to the central laboratory only for subjects who will be randomized; do not send samples from subjects who fail screening.

<sup>b</sup> Further instructions are provided in Appendix B.

<sup>c</sup> Anaerobic testing of cSSTI specimens and blood is required at sites where it is a local standard of care.

### 10.5 Lesion Measurements and Assessment of Signs and Symptoms of Disease (Investigator Blinded to Treatment)

Thoroughly examine the primary cSSTI site

- Measure the lesion size as directed in Appendix A
- Record all signs and symptoms of cSSTI as directed in Appendix E
- Ask the subject to rate their level of pain as directed in Appendix D; this may be performed by unblinded study personnel
- At the EOT and TOC Visits, perform an assessment of clinical response (Table 5)

- At the LFU Visit, perform an assessment of clinical relapse ([Table 7](#)); a telephone interview is acceptable for subjects who do not have symptoms of clinical relapse, ongoing AEs, new or ongoing SAEs, or laboratory abnormalities that require an on-site follow-up visit with a healthcare provider. If telephone interview, the assessment may be based on subject's report.

## 10.6 Samples for Pharmacokinetic Assessment

**Day 1:** Collect 2 blood samples after study drug administration (tedizolid phosphate arm only). The time points depend on the route of administration of dosing:

Subjects receiving IV tedizolid phosphate on the first day:

- 1 sample between 5 minutes and 80 minutes after
- 1 sample between 4 and 12 hours after

Subjects receiving oral tedizolid phosphate on the first day:

- Two samples between 4 and 12 hours after dosing, at least 60 minutes apart

**48 to 72 Hour Visit:** Collect 2 blood samples (regardless of route of dosing)

- 1 sample prior to study drug administration (within 60 minutes prior to administration)
- 1 sample between 4 and 12 hours after completion of administration

**Day 7:** Collect 1 blood sample at any time

Detailed instructions on collecting and processing blood PK samples are provided in Appendix G and the PK manual. Results of analysis will be reported separately.

## 11.0 ASSESSMENT OF SAFETY

The primary objective of this study is to compare the safety of IV and/ or oral 6-day 200 mg tedizolid phosphate with 10-day IV and/or oral Comparator in subjects 12 to <18 years with cSSTI. A DSMB will review safety data (eg, AEs and laboratory data) while the clinical trial is ongoing. Additional details are provided in the DSMB Charter. The central clinical laboratory will identify and note any values outside of the reference ranges, and sites will be notified of values of clinical significance by fax or electronic mail, with a follow-up telephone call if necessary. See Safety Investigator Laboratory Manual for additional information.

### 11.1 Safety Parameters

The timing of safety assessments is provided in [Table 3](#).

#### 11.1.1 Samples for Laboratory Evaluation for Safety

Obtain clinical laboratory samples and send to the local laboratory for pregnancy testing and, for subjects who are randomized, **also** send samples to the central laboratory, as shown in [Table 11](#). A list of laboratory tests is provided in Appendix F.

Table 11: Samples for Safety Laboratory Assessments

Sample	Laboratory		Comments
	Local	Central <sup>a</sup>	
<b>Blood</b>			
Hematology/differential		×	
Serum chemistry panel		×	
Pregnancy <sup>b</sup>	Screening Visit	Screening Visit EOT Visit	All females of childbearing potential
<b>Urine (Screening only)</b>			
Urinalysis		×	

<sup>a</sup> The study site is to send samples to the central laboratory only for subjects who will be randomized; do not send samples from subjects who fail screening

<sup>b</sup> Local pregnancy test may be conducted using a urine pregnancy test, provided the local test is one with high sensitivity (ie, has the ability to detect 10 mIU/mL hCG).

## 11.2 Adverse and Serious Adverse Events

### 11.2.1 Definition of Adverse Events

According to US Code of Federal Regulations (CFR), Title 21, 312.32 (21 CFR 312.32) (a) effective March 28, 2011 and FDA draft guidance “Safety Reporting Requirements for INDs and BA/BE Studies” issued September 2010, an AE is defined as follows:

“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 and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug and from any route of administration, formulation, or dose, including an overdose.”

Medical conditions present at baseline are considered medical history, and not AEs. However, any worsening of a pre-existing medical condition during the AE reporting period is to be reported as an AE.

### Suspected Adverse Reaction

A suspected adverse reaction is defined as follows:

“Any adverse event for which there is a reasonable possibility (evidence to suggest a causal relationship) that the drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.”

## Adverse Reaction

An adverse reaction is defined as follows:

“A subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.”

### Unexpected

An AE is considered unexpected if “it is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater severity) if the investigator brochure listed only cerebral vascular accidents. ‘Unexpected’, as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure 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”.

### Serious

A serious AE is defined as follows:

“If, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- In-patient hospitalization (*excluding hospitalization prior to randomization due to initial management of cSSTI at baseline and new hospitalizations due to progression of the underlying primary cSSTI lesion*) or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.”

Hospitalizations due to progression of the underlying primary cSSTI lesion are not considered SAEs.

### Life Threatening

An AE is considered life threatening “if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.”

### Pretreatment AE

A pretreatment event is an untoward medical occurrence in a clinical investigational subject who has signed the ICF to participate in a study but has not yet received the first infusion of study drug; it does not necessarily have any causal relationship with study participation. If a subject experiences a worsening or complication of a pretreatment condition or AE after receiving study drug, the worsening or complication is to be recorded as a TEAE. Investigators are to ensure that the AE term recorded captures the change in condition (eg, “worsening of...”).

### Treatment Emergent AE

An event that emerges, or a pre-existing event that worsens, any time after the subject receives the first dose of study drug through the end of the AE reporting period.

#### 11.2.2 Relationship to Study Drug

The Investigator will make a determination of the relationship of the AE to the study drug using a 4-category scale (not related, possible, probable, or definite) according to the following definitions:

Category	Definition
Not Related	AE does not follow a reasonable temporal sequence from study drug administration and can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment
Possible	AE follows a reasonable temporal sequence from the study drug administration (including the course after study drug withdrawal) and cannot be excluded as possibly being caused by study drug (eg, existence of similar reports attributed to the suspected drug and/or its analogues; reactions attributable to the pharmacologic effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable
Probable	AE follows a reasonable temporal sequence from study drug administration (including the course after study drug withdrawal) and can be excluded as possibly being caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment
Definite	AE follows a reasonable temporal sequence from study drug administration (including the course after study drug withdrawal), follows a known or hypothesized cause-effect relationship, and (if appropriate) satisfies the following: <ul style="list-style-type: none"><li>• positive results obtained in drug sensitivity tests</li><li>• toxic level of the drug present in blood or other body fluids</li></ul>

### 11.2.3 Recording Adverse Events

The Investigator will be responsible for ensuring that all AEs occurring during the AE reporting period are reported. The following information is to be recorded for each event and evaluation should be performed by a qualified physician: onset and stop dates, duration, severity, seriousness, causality, action taken, and outcome.

Medical conditions present at the time the ICF is signed are considered medical history and not AEs. However, any worsening of a pre-existing medical condition during the AE reporting period is to be reported as an AE.

Laboratory test and vital sign abnormalities will be reported as AEs only if the event leads to medical intervention (eg, additional concomitant medication, discontinuation of study drug).

All TEAEs that, in the opinion of the Investigator, may be infusion related should be identified as such on the AE e-CRF. Examples of infusion-related TEAEs are erythema, pain, induration, swelling, or phlebitis at the infusion site that is not related to mechanical malfunction of the infusion apparatus or to the venous puncture. Infusion intolerability is to be distinguished from TEAEs related to IV line placement procedures.

Categorize the severity of each AE as follows:

Severity	Definition
Mild	Minor and does not cause significant discomfort to subject or change in activities of daily living (ADL); subject aware of symptoms but symptoms easily tolerated
Moderate	An inconvenience or concern to subject and interferes with ADL, but subject able to continue with ADL
Severe	Significantly interferes with ADL and subject is incapacitated and/or unable to continue with ADL

### 11.2.4 Reporting Adverse Events

Subjects are to be monitored for AEs from signing of the ICF through 30 days after last study drug administration (AE reporting period). Ongoing AEs will be evaluated and documented. SAEs are to be followed using the SAE report form until stabilization, resolution/death, or consent is withdrawn.

Study site personnel are to ask subjects neutral questions when they are assessing the subject for AEs (eg, "How are you feeling?" or "Have you noticed any changes in your health?").

Investigators are to report all SAEs (excludes hospitalization prior to randomization due to initial management of cSSTI at baseline and events considered related to the primary cSSTI) that occur during the reporting period within 24 hours after becoming aware of the SAE to Sponsor Pharmacovigilance or its designee, IQVIA (formerly Quintiles).

- All initial and follow-up SAE Reports are to be transmitted via PPD
- Regional numbers are provided on the SAE form.

The SAE form, which is to be completed in English and signed by the Investigator (or appropriately qualified designee), is to include as much information as possible, but at a minimum must contain the following:

- A short description of the event and the reason why the event was categorized as serious
- Subject identification number
- Investigator's name
- Name of the study drug(s)
- Causality assessment

The timelines and procedures for SAE follow-up reports are the same as those for the initial report.

Copies of expedited reports for SAEs that are unexpected and at least possibly related to the study treatment will be sent to all concerned regulatory authorities, active Investigator(s), and the IRBs/ECs in accordance with local and site-specific requirements.

Further instructions with country-specific information are provided in the Safety Management Plan.

Sponsor or designee will be responsible for reporting suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities including the FDA, EMA, Investigators, and, for all active Investigators located in Europe, to central or local ECs and local competent authorities, as applicable, in accordance with national regulations in the countries where the study is conducted. SUSARs will be submitted within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations.

### 11.3 Pregnancy

Record pregnancy on Sponsor or designee's pregnancy form. Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Monitor the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) for a minimum of 30 days or until the first well-baby visit. Report congenital anomalies/birth defects and spontaneous miscarriages as SAEs. Elective terminations without complications are not AEs.

If the subject gives permission for her primary physician to be informed, the Investigator is to notify the subject’s primary physician that she was participating in a clinical study at the time she became pregnant, and Sponsor will provide details of the treatment the subject received.

## 12.0 STATISTICS

### 12.1 Analysis Sets

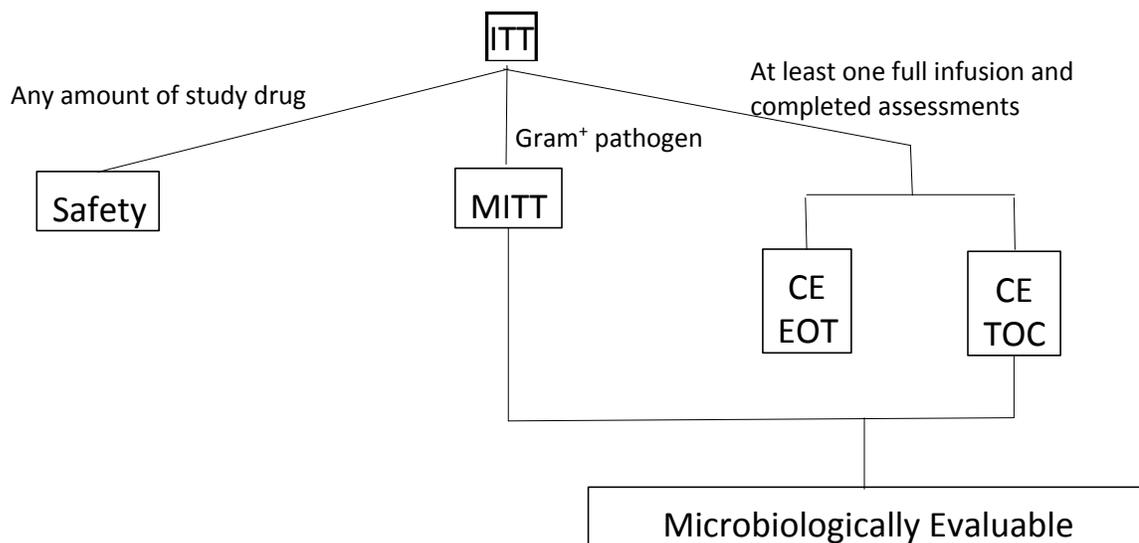
Analysis sets are defined in [Table 12](#) and the relationship between the 6 analysis sets is shown in [Figure 3](#).

Table 12: Analysis Sets

Analysis Set	Definitions
Intent to Treat (ITT)	Data from randomized subjects
Safety	Data from randomized subjects who received any amount of study drug
Microbiological ITT (MITT)	Data from randomized subjects who have a baseline gram-positive bacterial pathogen known to cause cSSTI
Clinically Evaluable at End of Therapy (CE-EOT)	Data from randomized subjects receiving at least one full infusion of study drug who complied with the protocol with no major violations, as defined in the statistical analysis plan, and who meet the following criteria: <ul style="list-style-type: none"> <li>completed EOT Blinded Investigator’s assessments</li> <li>had no concomitant systemic antibiotic therapy from the first infusion of study drug through the EOT Visit that is potentially effective against the baseline pathogen except adjunctive AZ and/or MNZ in subjects with wound infections</li> </ul>
CE-Test of Cure (CE-TOC)	Data from randomized subjects receiving at least one full infusion of study drug who complied with the protocol with no major violations, as defined in the statistical analysis plan, and who meet the following criteria: <ul style="list-style-type: none"> <li>completed EOT and TOC Blinded Investigator’s assessments (unless assessed as failures at any time point before the TOC Visit)</li> <li>had no concomitant systemic antibiotic therapy from first infusion of study drug through TOC Visit that is potentially effective against baseline pathogen except adjunctive AZ and/or MNZ in subjects with wound infections</li> </ul>
Microbiologically Evaluable (ME)	Data from subjects in the MITT Analysis Set who are also in the CE-TOC Analysis Sets

Abbreviations: AZ=aztreonam; cSSTI=complicated skin and soft tissue infection; EOT=end of therapy; MNZ=metronidazole; TOC=test of cure.

Figure 3: Analysis Sets



Abbreviations: CE=clinically evaluable; EOT= end of therapy; TOC=test of cure; ITT=intent to treat; MITT=microbiological intent to treat.

### 12.1.1 Process for Determining Inclusion in Analysis Sets

Inclusion into the ITT and Safety Analysis Sets will be determined programmatically from the e-CRF data. Inclusion into the CE Analysis Set will be determined programmatically from the e-CRF data and the manual review conducted by the ERT. The ERT may review subject data to confirm that analyses set criteria are satisfied.

Inclusion into the MITT Analysis Set will be determined programmatically by incorporating the outcome of the review of the isolates by the ERT. The ERT will determine whether each isolate is considered a pathogen based on a review of information regarding baseline samples including infection type, type of specimen, Gram stain results, and local and central laboratory genus and species identification. Inclusion into the ME Analysis Set will be determined programmatically.

### 12.2 Sample Size

The primary objective of the study is to determine the safety of tedizolid phosphate. Thus, the study is not powered for inferential statistics. Rather, a sufficient number of subjects are being randomized to provide an initial characterization of the safety of tedizolid phosphate in subjects 12 to <18 years of age.

### 12.3 General Statistical Considerations

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for

continuous variables will be provided. All comparisons will be for tedizolid phosphate versus Comparator.

Exploratory analyses may also be performed. Listings of individual subject's data will be produced. A comprehensive statistical analysis plan (SAP) will be submitted to regulatory authorities, as appropriate, prior to initiation of the study.

### **12.3.1 Subject Population and Characteristics**

Enrollment, protocol deviations/violations, and discontinuations from the study drug and the study will be summarized by treatment group. Demographics (age, race, sex), medical and surgical history, description of the cSSTI, baseline assessment of the clinical signs and symptoms, and microbiological assessment of the primary infection site will be summarized by treatment group. Differences between treatment groups will be analyzed using the chi-square or Fisher's exact test for dichotomous variables and the Wilcoxon Rank Sum test for ordinal variables and continuous variables.

### **12.3.2 Study Drug Exposure**

A study drug administration summary by treatment group will be provided including the distribution of the total number of study drug administrations, the number of IV administrations, and the number of oral administrations. Treatment compliance will be estimated based on the number of active study drug administrations a subject is expected to receive. Descriptive statistics will be presented for treatment compliance and differences between the treatment groups will be assessed using a Wilcoxon Rank Sum test. The number of IV administrations received prior to switching to oral study drug will be summarized. Differences between treatment groups will be determined using the Wilcoxon Rank Sum test.

## **12.4 Efficacy Analyses (Primary, Secondary, Additional)**

For all efficacy analyses, subject data will be analyzed in the group to which the subject was randomized. By definition, subjects who receive the study drug from the treatment group to which they are not randomized are not included in the CE-EOT, CE-TOC, and ME Analysis Sets.

### **12.4.1 Primary Efficacy Analysis**

The primary efficacy outcome is the Blinded Investigator's assessment of clinical success at the TOC Visit in the ITT and CE-TOC Analysis Sets. A subject assessed as a clinical failure at any time during the study is considered a clinical failure at the TOC Visit. Response definitions for the Blinded Investigator's assessments are defined in [Table 5](#).

The number and percentage of subjects who have a Blinded Investigator's assessment of clinical success, clinical failure, and indeterminate response at TOC in the ITT and CE-TOC (by definition, subjects in the CE-TOC cannot have an indeterminate response) Analysis Sets will be determined for each treatment group. An exact two-sided 95% confidence interval (CI) will be determined for the rate of clinical success in each treatment group using the Clopper-Pearson method. The difference in the rate of clinical success will

be determined as will a two-sided 95% CI for the difference using the unstratified method of Miettinen and Nurminen.

#### **12.4.2 Secondary Efficacy Analyses**

Secondary efficacy outcomes are listed in Section 10.1. Descriptive statistics, exact two-sided 95% CIs for the point estimates of success, and two-sided 95% CIs for the difference in success rate will be provided for all the secondary outcome measures.

#### **12.4.3 Additional Efficacy Analyses**

Additional efficacy analyses will be conducted to support the efficacy findings of the primary and secondary efficacy outcomes and are listed in Section 10.1. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided.

The number and percentage of subjects in the CE-TOC analysis set who relapsed at the LFU Visit will be presented for those subjects who were a clinical success at the TOC Visit. In addition, the number and percentage of subjects in each treatment group with a superinfection or a new infection will also be provided.

### **12.5 Safety Analyses**

Safety will be assessed through summaries of TEAEs, laboratory evaluations (hematology and chemistry), vital signs, cSSTI procedures, concomitant medications, and physical examinations, including a basic neurologic examination with cranial nerve assessments. All safety analyses will be based on the Safety analysis set, and will be summarized for each treatment group. Subjects who receive the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received.

#### **12.5.1 Adverse Events**

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events reported after the ICF is signed but before the first infusion of study drug is administered (pretreatment AEs) will be collected and presented in a listing; no analyses will be performed. Summary tables of TEAEs will be provided. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of any TEAE leading to study drug discontinuation, infusion-related TEAEs, and SAEs will be provided.

#### **12.5.2 Laboratory Evaluations**

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. The change from baseline to each postbaseline visit and to the overall worst postbaseline value will also be summarized by treatment group. Laboratory values will be classified according to a modified *Division of Microbiology and Infectious Diseases Adult Toxicity Scale, November 2007* criteria and shifts in toxicity grade from baseline to postbaseline will be summarized. Selected laboratory values will also be

classified as substantially abnormal from normal limits and summary data presented for the worst postbaseline value.

### 12.5.3 Handling of Missing Data

Missing values will not be imputed for primary and secondary efficacy and safety analyses (except as detailed in the SAP for missing dates) and only observed values will be used in data analyses and presentations.

For the primary efficacy outcome measure of Blinded Investigator’s assessment of clinical response at the TOC Visit, if any component of the outcome measure, for example, assessment of signs and symptoms at the TOC Visit, is missing, the subject will be assigned a response of indeterminate. For the analysis in the ITT Analysis Set, indeterminates are included in the denominator and are thus considered clinical failures. By definition, data from subjects with an indeterminate response are excluded from the CE-EOT Analysis Set.

For the primary efficacy outcome measure of Blinded Investigator’s assessment of clinical response at the TOC Visit, when there are missing data at the EOT or TOC Visits the response is categorized as defined in [Table 13](#).

Table 13: Blinded Investigator’s Assessment of Clinical Response Determination Considering Missing Data

EOT Visit	TOC Visit	Investigator Assessment of Clinical Response at TOC
Missing (indeterminate)	Success	Indeterminate
Missing (indeterminate)	Failure	Failure
Missing (indeterminate)	Missing (indeterminate)	Indeterminate
Success	Missing (indeterminate)	Indeterminate
Failure	Missing (indeterminate)	Failure

Abbreviations: EOT=end of therapy; TOC=test of cure.

A sensitivity analysis of the primary efficacy outcome in the ITT Analysis Set will be conducted in which subjects with an indeterminate response are considered Success.

For the secondary outcome measure of programmatic determination of early clinical response at the 48-72 Hour Visit in the ITT Analysis Set, if any data field needed to determine the response is missing the subject will be assigned an indeterminate response. For analyses of the secondary outcome, subjects with an indeterminate response are included in the denominator, and thus, are considered nonresponder, ie, Failures.

For the analysis in the ITT Analysis Set of Blinded Investigator’s assessment of clinical response at TOC, indeterminate outcomes are included in the denominator and are thus considered clinical failures. By definition, subjects with an indeterminate response are excluded from the CE-TOC Analysis Set.

Missing data are handled in a similar manner for the outcome of microbiological response at the TOC Visit.

#### **12.5.4 Protocol Deviations**

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Protocol deviations are variations from the protocol and will be recorded and categorized by the type of deviation, including subjects with the following:

- those who entered the study even though they did not satisfy all entry criteria
- those who developed withdrawal criteria during the study but were not withdrawn
- those who received the wrong treatment or incorrect dose
- those who received an excluded concomitant treatment

### **13.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

#### **13.1 Study Monitoring**

Before an investigational site can enter a subject into the study, a representative of Sponsor will visit the investigational study site for the following reasons:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of Sponsor or its representatives. This will be documented in a Clinical Study Agreement between Sponsor and the Investigator

During the study, a monitor from Sponsor or representative will have regular contacts with the investigational site for the following reasons:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the e-CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts)

- Record and report any protocol deviations not previously sent to Sponsor
- Confirm AEs and SAEs have been properly documented on e-CRFs and confirm SAEs have been forwarded to Sponsor and those SAEs meeting the criteria for reporting have been forwarded to the IRB

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

### **13.2 Audits and Inspections**

Sponsor personnel or their designee may perform an audit at any time during or after completion of the clinical study. All study-related documentation is to be made available to the designated auditor. In addition, study site personnel are to be available to answer any questions. The Investigator will permit authorized representatives of Sponsor and the regulatory agencies or local health authorities to inspect facilities and records relevant to this study. The Investigator should contact Sponsor immediately if contacted by a regulatory agency about an inspection.

### **13.3 Case Report Forms and Study Records**

The site will be supplied with the following data collection tool: a web browser address for an Electronic Data Capture (EDC) system that has been fully validated and conforms to (US Code of Federal Regulations, Title 21, Part 11: Electronic Records; Electronic Signatures) (21 CFR Part 11) and the Guidance for Industry on Computerized Systems Used in Clinical Trials requirements. The EDC system will be maintained by a Contract Research Organization (CRO).

The trained Investigator site staff will enter the data required by the protocol into the eCRF from source documents (eg, medical records and study-specific data capture forms as needed) into the EDC system. All information on the e-CRFs must be traceable to these source documents. Data recorded directly on the e-CRFs will be defined before study start.

E-CRFs will be completed for all enrolled subjects. Informed consent, demography, inclusion/exclusion and end of study e-CRF pages are needed for subjects who are enrolled but not treated. A clinical monitor will review the e-CRFs entered by investigational staff for completeness and accuracy.

All data changes will be clearly indicated with a means to locate prior values. A unique user identification and password to enter or change data will be assigned in order to prevent unauthorized access to the data.

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. The computerized system is able to generate accurate and complete copies of records in paper or electronic form for inspection and review by applicable regulatory authorities, the IRB/EC/REB, and auditors or other designees authorized by Sponsor.

In addition to capturing the user identification as part of the audit trail for all data entry, the e-CRF allows for application of electronic signatures. The Investigator or designated sub investigator, following review of the data in the e-CRF, will confirm the validity of each subject's data by electronic signature. This electronic signature will be certified as outlined in 21 CFR Part 11.

Sponsor will retain the original e-CRF data and audit trail. An electronic or certified paper copy of all completed e-CRF data, including query resolution correspondence, will be provided to the Investigator at the end of the study.

#### **13.4 Institutional Review Board/Ethics Committee/Research Ethics Board**

In accordance with US regulations and the ICH guidance, the Investigator is responsible for submitting the study protocol, sample ICF, and any other documents that pertain to subject information (ie, subject dosing diary), recruitment methods such as advertisements, and any other information that may be requested to the IRB/EC/REB for review and approval prior to initiation of the study. The IRB/EC/REB will provide the Investigator written assurance of compliance with ICH (E6) guidelines.

The Investigator shall obtain and maintain records for all written IRB/EC/REB approval documentation including reviews of any subsequent changes to the study (ie, protocol amendment(s) or modifications to the ICF). The Investigator will obtain annual IRB/EC/REB approval at appropriate intervals as required not to exceed 1 year and at the close of the study.

The Investigator must report unanticipated problems involving risks to subjects or others, serious and/or continuing noncompliance, and any suspension or termination of Investigator participation in the study to the IRB/EC/REB promptly according to the IRB/EC/REB requirements.

#### **14.0 QUALITY CONTROL AND QUALITY ASSURANCE**

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Sponsor may conduct a quality assurance audit. Please see Section 13.2 for more details regarding the audit process.

##### **Data Quality Assurance**

Logic and consistency checks are to be performed on all data entered into the e-CRFs to ensure accuracy and completeness. Laboratory results (blood and microbiological samples) are to be obtained from the central laboratory and transferred electronically to Sponsor or designee.

Training sessions, regular monitoring of investigators by Sponsor or designated personnel, instruction manuals, data verification, cross-checking and data audits will be performed to ensure quality of all study data. Investigator meetings and/or on-site site initiations will be performed to prepare Investigators and other study personnel for appropriate collection of study data.

Automatic validation programs or manual checks for data discrepancies in the e-CRFs may result in electronic queries generated for resolution by the investigational site. Designated

site staff are required to respond to these queries and make any necessary changes to the data. Audits for quality assurance of the database may be performed according to relevant Standard Operating Procedures within the CRO or at the request of Sponsor Quality Assurance department.

## **15.0 ETHICS**

### **15.1 Ethical Conduct of the Study**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with applicable United States FDA clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the EU Directive 2001/20/EC for clinical trials conducted in the EU, and the IRB/EC/REB and local legal requirements.

Each Investigator is to adhere to GCPs, regulatory guidelines, local laws and regulations, and the protocol as detailed in this document. The Investigator must obtain written approval of any changes to the protocol from Sponsor prior to seeking approval from the IRB/EC/REB. Each Investigator will be responsible for enrolling only subjects who meet protocol inclusion and exclusion criteria.

### **15.2 Written Informed Consent**

The Investigator should use the Sponsor-approved ICF template to incorporate any site-specific information. No deletions or major deviations are to be made to the draft ICF without prior written approval from Sponsor or designee. Any changes required by the IRB/EC/REB will require Sponsor or designee review and agreement prior to use. The Investigator will provide Sponsor with a copy of the consent form and assent form which was reviewed and approved by the IRB/EC/REB.

The Investigator or trained designee is to explain the study and ICF to the subject/LAR and answer any questions in accordance with US Code of Federal Regulations, Title 21, Part 50: Protection of Human Subjects (21 CFR Part 50). The subject/LAR is to sign and date the ICF before any study specific procedures are performed. The person who conducts the informed consent discussion is to sign and date the ICF and provide a fully executed copy to the subject/LAR. If applicable, an IRB/EC/REB approved certified translation of the ICF in a language understandable to the subject/LAR will be provided. The subject's parent(s) or LAR are to sign and date the ICF and assent will be obtained from adolescents capable of understanding the nature of the study before protocol-specific procedures are carried out.

The original signed and dated ICF is to remain in each subject's study file and be available for review by study monitors or authorized regulatory representatives at any time.

### **15.3 Subject Confidentiality**

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted is prohibited.

Information obtained during the conduct of this study will be collected, processed, and transmitted to or for the benefit of Sponsor in accordance with applicable law, as discussed below. Information contained therein will be maintained in accordance with applicable law protecting subject privacy and may be inspected by the clinical researcher, the researcher's staff, Sponsor and its representatives, to check, process, evaluate, and use the information collected during the study. Processing, evaluation, or use of the information will be performed by a health professional for medical purposes and/or by those operating under a duty of confidentiality that is equivalent to that of a health professional. Information will be transmitted and processed as Sponsor may direct, including to Sponsor and its representatives in the United States or elsewhere. Information obtained from the study will likely be used by Sponsor in connection with study drug development, including possible filing of regulatory dossiers with governmental authorities for marketing approval, and for other pharmaceutical and medical research purposes. The Investigator is obliged to provide Sponsor with complete test results and all data developed in this study. This information may be disclosed to other physicians who are conducting similar studies, to the FDA/applicable regulatory agencies as deemed necessary by Sponsor or to local health authorities as required by law. Subject-specific information may be provided to other appropriate medical personnel only with the subject/LAR's permission.

All Investigators and other research study personnel who process information from the study must take appropriate measures to prevent unauthorized or unlawful processing or disclosure of data.

To ensure compliance with current US Regulations and the ICH GCP E6 guideline, data generated by this study including source documentation must be available for inspection upon request by representatives of the FDA, national and local health authorities, Sponsor and the IRB/EC/REB for each study site.

## **16.0 DATA HANDLING AND RECORDKEEPING**

### **16.1 Inspection of Records**

Sponsor or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **16.2 Retention of Records**

The Investigator is to retain records and documents pertaining to the conduct of this study including PDF copies of e-CRFs, source documents, ICFs, laboratory test results, and study medication inventory records for a period of 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 the investigational product. No study records shall be destroyed without prior authorization from Sponsor.

## **17.0 PUBLICATION POLICY**

Sponsor intends to pursue publication of the results of the study in cooperation with a lead

Investigator, subject to the terms and conditions of the clinical study agreement between Sponsor and Investigators. Sponsor approval in writing is required for publication of any data subsets. Eligibility for authorship will be determined in accordance with the International Committee of Medical Journal Editors definition of authorship (ie, requiring substantial contributions to study conception, study design, enrollment, data analysis, and/or interpretation of the results) (<http://www.icmje.org/>). Subject names and other personal data relating to an identified or identifiable subject (such as photographs, audio, videotapes, or other factors specific to physical, physiological, mental, economic, cultural or social identity), may not be disclosed in any publication without prior written authorization from Sponsor and the subject.

## **18.0 REFERENCE LIST**

None.

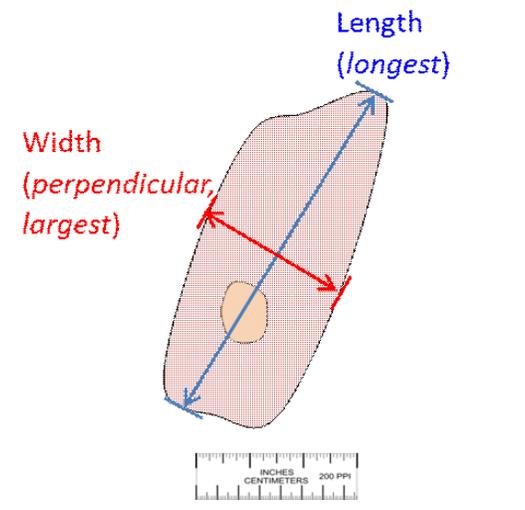
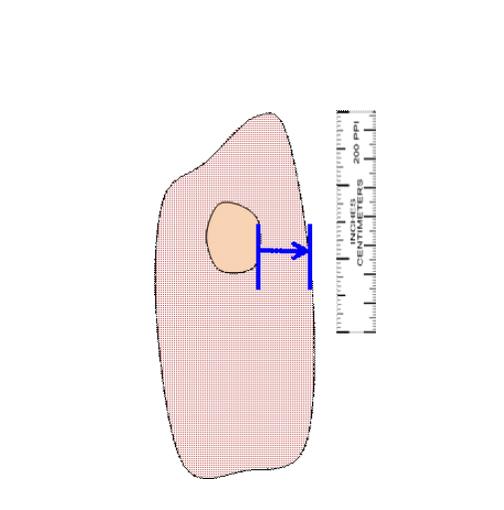
## **19.0 APPENDICES**

**APPENDIX A. SITE INSTRUCTIONS FOR PRIMARY CSSTI SITE MEASUREMENT**

**Measurement of Lesion size (longest dimension and lesion area):**

1. Length of erythema, edema, or induration (EEI) should be measured, as of protocol amendment 3, along the *longest* dimension, regardless of the orientation with the axis of the body or limb (**Note that this is different from measurements for the original protocol and amendments 1 and 2**). This reflects the modified inclusion criteria for lesion size, which now require the lesion to extend at least 4 cm in 1 dimension. Width is measured as the greatest width perpendicular to the longest length, as shown in the figure below. Note: in subjects with darker skin, the perimeter of EEI 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.
3. A surface area (cm) will be calculated by the e-CRF. This is no longer an inclusionary criterion, however, it is needed for assessment of the secondary endpoint (reduction in lesion size at 48-72 hours).

**Measurement of Margin:** As of amendment 3, there is no longer an inclusion requirement for EEI extending at least 2 cm shortest distance from the peripheral margin of the abscess or wound. However, this measurement is still recorded on the eCRF. The method for measurement has not changed, and is shown graphically below.

<p>Measure longest lesion dimension (length), regardless of orientation to the body, and the longest width perpendicular to that length.</p>	<p>Measure <i>smallest</i> margin from edge of abscess or wound to the perimeter of Erythema, Edema, and/or Induration</p>
	

## **APPENDIX B. MICROBIOLOGICAL SAMPLING AND PATHOGEN DETERMINATION**

Appropriate specimens (aspirates, biopsy, deep swabs, etc.; superficial swabs are not acceptable) of the primary cSSTI site and blood will be collected at various time points (see [Table 3](#) Study Design and Schedule of Assessments). Specimens are required for abscesses and wounds at Screening; cellulitis specimens are to be collected according to standard practice at the site.

Specimens from the primary cSSTI site should be sent to the site's local laboratory for Gram stain and culture (including anaerobic culture at sites where this is a standard of care). Blood samples should be sent to the site's local laboratory for culture (Gram stain optional). Blood cultures for anaerobic pathogens are required at sites where it is a local standard of care. Isolates should be identified using the local laboratory's usual procedures. All unique organisms from the cSSTI site and/or blood samples will be stored and sent to the Sponsor designated central laboratory for confirmation of identification and susceptibility testing.

Backup samples of all organisms isolated from the cSSTI site and of blood should be stored frozen at each site's local laboratory. The local laboratory should store these backup samples until the site/Investigator is notified by Sponsor to discard them or ship them to Sponsor designated Central Laboratory.

Additional information is provided in the Microbiology section of the Laboratory Manual.

### **Gram Stain Requirements**

Gram stains should be read and reported per your institution's procedures so that required Gram stain data can be recorded on the e-CRF.

Report the presence of WBCs as follows:

- No WBCs
- 1 to 5 WBCs per low power field
- 6 to 10 WBCs per low power field
- $\geq 11$  WBCs per low power field

### **Pathogen Determination**

Pathogen determination is based on the genus and species identification from the central laboratory. Three categories of pathogen classification are defined as follows:

1. Always a pathogen: If the organism was isolated from the culture of the cSSTI, the following are always considered a pathogen:

Monomicrobial infections caused by any of the following:

*Staphylococcus aureus*

*Staphylococcus haemolyticus*

*Staphylococcus lugdunensis*

Group A and B  $\beta$ -hemolytic streptococci (eg, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus pyogenes*)

*Streptococcus anginosus-milleri* group (eg, *Streptococcus anginosus*,  
*Streptococcus intermedius*, *Streptococcus constellatus*)

*Enterococcus faecalis*

*Enterococcus faecium*

Gram-positive anaerobes

Polymicrobial infection is defined as a skin infection caused by more than 1 pathogen, including 1 that is identified in the above mentioned “Monomicrobial Infections” list. All infections with  $\geq 2$  pathogens or with a pathogen not on the “Monomicrobial Infection” list will be reviewed on a case-by-case basis.

2. Never a pathogen: If the organism was isolated from the culture of the cSSTI, the following are never a pathogen:

*S. saprophyticus*

*Corynebacterium* spp.

*S. epidermidis*

*Bacillus* spp.

*Diphtheroids*

*Micrococci*

*Candida* spp., *Aspergillus* spp., or other fungi

3. Case-by case review: All isolates not defined by criterion 1 or 2 above will be assessed case-by-case with a manual review by Sponsor. If needed, subject clinical (eg, type of infection, type of specimen, subject underlying conditions, etc.) and microbiological information (eg, Gram stain, etc.) will be used to assist in determining if the isolate is a pathogen. All organisms isolated from a blood culture and all gram-negative organisms will be reviewed by Sponsor to determine if the organism is a pathogen.

**APPENDIX C. NEUROLOGIC AND CRANIAL NERVE EXAMINATION\***

Perform a neurological examination including assessments of sensation, alertness, peripheral reflexes (biceps, patellar tendon, ankle jerk, and plantar response), muscle tone and strength (upper and lower limbs), coordination (finger to nose) and tremor of the hands/fingers. All assessments will be graded as normal or abnormal.

NOTE: Assessment of the olfactory nerve is optional: such data is subject to individual perception and there is a heightened potential for external interference, eg, allergies, rhinitis or upper respiratory infection. Olfactory nerve impairment has not been reported for oxazolidinones to date.

<b>Cranial Nerve Assessment</b>			
<b>Nerve</b>	<b>Name</b>	<b>Function</b>	<b>Test (examples)</b>
<b>I</b>	Olfactory*	Smell	Have subject smell a familiar odor
<b>II</b>	Optic	Visual field	Check peripheral vision
<b>III</b>	Oculomotor	Pupillary Reaction	Shine light in the eye
<b>IV</b>	Trochlear	Eye Movement	Have subject follow a finger without moving the head
<b>V</b>	Trigeminal	Facial Sensation; Motor Function	Touch the face; Have subject hold mouth open
<b>VI</b>	Abducens	Motor Function	Check lateral eye movements
<b>VII</b>	Facial	Motor Function; Taste	Have subject smile, wrinkle face, puff cheeks; Evaluate taste
<b>VIII</b>	Acoustic	Hearing; Balance	Snap fingers by the ears; Romberg's test
<b>IX</b>	Glossopharyngeal	Swallowing and Voice	Have subject swallow and say "Ah"
<b>X</b>	Vagus	Gag Reflex	Use tongue depressor to evaluate
<b>XI</b>	Spinal Accessory	Neck Motion	Evaluate shoulder shrugging
<b>XII</b>	Hypoglossal	Tongue Movement and Strength	Have subject stick out tongue; apply resistance with a tongue depressor

\*Olfactory nerve assessment is optional.

## APPENDIX D. PAIN EVALUATION

Pain will be evaluated using the Wong-Baker Faces Rating Scale (FRS) throughout the study (see Table 3). Explain to the subject that the purpose of the tool is to understand the amount of pain they are experiencing, determine if the pain medication they are receiving is doing enough, and decide if anything more needs to be done.

Ask the subject to rate their level of pain using the FRS. Use this scale only once per time point.

### WONG-BAKER FACE SCALE FOR PAIN ASSESSMENT (SUBJECT USE)

Ask the subject to rate their pain: ‘How would you rate your pain at present out of 10, with 0 being no pain at all and 10 being the worst pain you could imagine?’ The subject can respond orally or by pointing to where they would rate their pain. Enter the numerical value on the e-CRF.



Modified from The Wong-Baker Pain FACES Scale Measures Pain, Not Fear. Garra G, Singer AJ, Domingo A, and Thode Jr HC. Ped Emer Care 2013; 29(1):17-20.

**APPENDIX E. SIGNS AND SYMPTOMS OF CSSTI**

Signs and symptoms will be assessed for the primary complicated skin and soft tissue infection site.

The Investigator is to provide a categorical assessment and comparison to baseline (improved, not improved) of the following parameters using the scale below:

- Erythema
- Swelling/edema
- Induration
- Localized warmth
- Pain or tenderness
- Drainage
- Fluctuance

	<b>Absent</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
Erythema	None	Pink	Red	Fiery red
Swelling/edema	None	Swelling just apparent on casual inspection (up to 2 mm of pitting)	Marked swelling ( $\leq 4$ 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 palpation	Uncomfortable with light palpation or pressure	Intolerable by even a mild stimulus such as sheet touching
Drainage	None	Serous	Seropurulent	Purulent

**APPENDIX F. CLINICAL LABORATORY EVALUATIONS**

<b>Clinical Laboratory Evaluations</b>	
<p><b>Chemistry Panel</b>                      Total Bilirubin                      Direct Bilirubin                      Indirect Bilirubin                      Albumin                      Alkaline phosphatase                      Alanine aminotransferase                      Aspartate aminotransferase                      Gamma-glutamyl transpeptidase                      Lactate dehydrogenase                      Urea nitrogen Creatinine                      Glucose                      Uric Acid                      Calcium                      Phosphorus                      Total Protein                      Cholesterol                      Creatine kinase/ creatine phosphokinase                      Sodium                      Potassium                      Bicarbonate                      Chloride                      Magnesium</p>	<p><b>Hematology/Differential Panel</b>                      Hemoglobin                      Hematocrit                      Red blood cell count                      White blood cell count                      Neutrophils (% absolute)                      Lymphocytes (% absolute)                      Monocytes (% absolute)                      Eosinophil's (% absolute)                      Basophils (% absolute) Bands (% absolute)                      Platelet count</p> <p><b>Pregnancy Test</b> (all females of childbearing potential)                      Serum beta-human chorionic gonadotropin; local <b>and</b> central laboratory at the Screening Visit. Local pregnancy test may be conducted using a urine pregnancy test, provided the local test is one with high sensitivity (ie, has the ability to detect 10 mIU/mL hCG)</p> <p><b>Urine Panel (Screening only)</b>                      pH                      Bilirubin                      Glucose                      Ketones                      Urobilinogen</p>

## **APPENDIX G. SAMPLES FOR PHARMACOKINETIC ASSESSMENT**

Blood will be collected from subjects receiving tedizolid phosphate to evaluate the systemic plasma concentrations of tedizolid and tedizolid phosphate after administration of tedizolid phosphate using a validated assay.

**Day 1:** Collect 2 blood samples after study drug administration (tedizolid phosphate arm only). The time points depend on the route of administration of dosing:

Subjects receiving IV tedizolid phosphate on the first day:

- 1 sample between 5 minutes and 80 minutes after dosing
- 1 sample between 4 and 12 hours after dosing

Subjects receiving oral tedizolid phosphate on the first day:

- Two samples between 4 and 12 hours after dosing, at least 60 minutes apart

**48 to 72 Hour Visit:** 2 blood samples

- 1 sample prior to study drug administration (within 60 minutes prior to administration)
- 1 sample between 4 and 12 hours after completion of administration

**Day 7:** Collect 1 blood sample at any time

Detailed information on sample collection and processing is provided in the PK section of the Laboratory Manual.

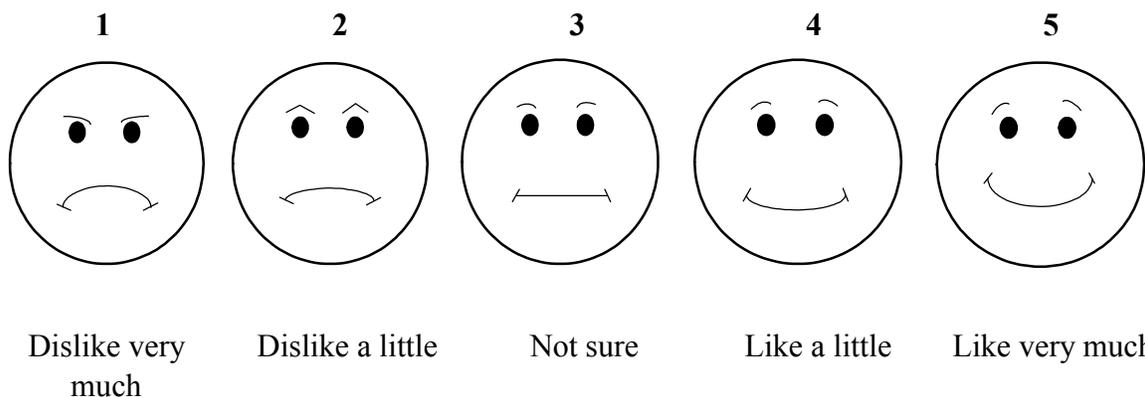
Perform the following:

1. Collect blood in the tube provided by the Sponsor-designated central laboratory
2. Slowly invert the tube at least 8 to 10 times
3. Place the tube in an ice water bath until centrifugation
4. Centrifuge the sample at  $2000 \times g$  at  $5^{\circ}\text{C}$  for 15 minutes. If a refrigerated centrifuge is not available, place the tube in an ice bath immediately before and after the centrifugation for at least 5 minutes each time
5. Collect the supernatant (plasma), split the sample into 2 aliquots and store at  $-70^{\circ}\text{C}$  (or at up to  $-20^{\circ}\text{C}$ ; however,  $-70^{\circ}\text{C}$  is preferred)
  - One aliquot will be shipped to the Sponsor-designated central laboratory. The other aliquot is to be stored at the study site as a back-up sample until notified by Sponsor or designee that the sample either is to be sent to the Sponsor-designated central laboratory or is to be destroyed

**APPENDIX H. PALATABILITY SCALE**

Palatability will be evaluated **one time only** using a 5-point hedonic scale within 30 minutes of the first oral administration.

Ask the subject to rate the taste of tedizolid phosphate tablets. The subject can respond orally or by pointing to a face. Enter the numerical value on the e-CRF.



Recreated from Taste Comparisons for Lansoprazole Strawberry-Flavoured Delayed Release Orally Disintegrating Tablet and Ranitidine Peppermint-Flavoured Syrup in Children. Tolia V, Han C, North J, Amer F. Clin Drug Invest 2005; 25(5):285-292.

**APPENDIX I. EXAMPLES OF PROHIBITED CONCOMITANT MEDICATIONS**

The following examples of prohibited concomitant medications are not all inclusive and should be used as a guide for exclusion from the protocol.

Receipt of the following medications is prohibited in the 2 weeks prior to study through the EOT Visit.

<b>Examples</b>		
<b>Monoamine Oxidase Inhibitors</b>		
Iprindole	Moclobemide	Rasagiline
Iproniazid	Nialamide	Selegiline
Iproclozide	Opipramol	Toloxatone
Isocarboxazid	Phenelzine	Tranylcypromin
<b>Selective Serotonin Reuptake Inhibitors</b>		
Citalopram	Fluoxetine	Sertraline
Dapoxetine	Fluvoxamine maleate	Vilazodone
Escitalopram oxalate	Paroxetine	
<b>Serotonin Norepinephrine Reuptake Inhibitors</b>		
Duloxetine	Desvenlafaxine	Venlafaxine
<b>Tricyclic Antidepressants</b>		
Amitriptyline	Doxepin	Protriptyline
Clomipramine	Imipramine	Trimipramine
Desipramine	Lofepramine	
Dosulepin	Nortriptyline	
<b>Triptans and other medications with potential serotonergic activity</b>		
Amoxapine	Mirtazapine	Trazodone
Bupropion	Naratriptan	Trimeperidine
Buspirone	Nefazodone	Zolmitriptan
Maprotiline	Rizatriptan	
Meperidine	Sumatriptan	