Official Protocol Title:	A Phase 3 Randomized, Active-comparator-controlled Clinical Trial to Study the Safety and Efficacy of MK-1986 (Tedizolid Phosphate) and Comparator in Subjects from Birth to less than 12 Years of Age with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)
NCT number:	NCT03176134
Document Date:	27-Jun-2022

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TITLE:

A Phase 3 Randomized, Active-comparator-controlled Clinical Trial to Study the Safety and Efficacy of MK-1986 (Tedizolid Phosphate) and Comparator in Subjects from Birth to less than 12 Years of Age with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

IND NUMBER: [106,307 (IV) *and* 125,076 (Oral Suspension)]
EudraCT NUMBER: 2016-003884-20

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 7	27-JUN-2022	Added a potential interim analysis for the 2 cohorts spanning 2 to <12 years of age in order to support a possible regulatory filing for this age group in light of the slower enrollment of children <2 years of age; reduced the sample size from 120 to 100; and revised eligibility criterion regarding allowed duration of prior antibiotic treatment.
Amendment 6	24-MAY-2021	Eliminated certain eligibility constraints and reduced the number of required in-person visits in order to improve feasibility to enroll outpatients.
Amendment 5	16-SEP-2020	Preplanned addition of dose levels for children 28 days to <2 years of age (Cohort 3) based on updated modeling and simulation using newly available data from ongoing studies; addition of country-specific eligibility requirements; and addition of study termination criteria and data protection policies.
Amendment 4	03-OCT-2019	Dosing adjustment due to a preplanned analysis.
Amendment 3	20-SEP-2018	Dose adjustment including modification to BID dosing; modified extension of treatment to allow 1-4 days of extension (not fixed at 4 days' extension); added recommendations for comparator dosing; modification of IC/EC; modification of procedures e.g. PK sampling to account for BID dosing regimen
Amendment 2	13-APR-2018	Reduced minimum age to birth; clarification of minimum sample sizes in each age group
Amendment 1	10-AUG-2017	Dose adjustment, addition of excluded medications, modification of IC/EC
Original Protocol	25-JUL-2016	Not applicable

SUMMARY OF CHANGES

PRIMARY REASONS FOR THIS AMENDMENT:

Added a potential interim analysis for the 2 cohorts spanning 2 to <12 years of age in order to support a possible regulatory filing for this age group in light of the slower enrollment of children <2 years of age; reduced the sample size from 120 to 100; and revised eligibility criterion regarding allowed duration of prior antibiotic treatment.

Section Numbers	Section Titles	Description of Changes	Rationale
8.1 8.6.1.1 8.6.2 8.7	Statistical Analysis Plan Summary Efficacy Endpoints Statistical Methods for Safety Analyses Interim Analyses	Added a potential interim analysis for Cohort 1, children 2 to 6 years of age, and Cohort 2, children 6 to <12 years of age, when these subjects complete the study.	To support a potential regulatory filing for this age group in light of the slower enrollment of children <2 years of age.
1.0 2.1 4.2.1 5.3 8.1 8.9 8.10	Trial Summary Trial Design Rationale for the Trial and Selected Subject Population Randomization or Treatment Allocation Statistical Analysis Plan Summary Sample Size and Power Calculations Subgroup Analyses and Effect of Baseline Factors	Updated the planned sample size from 120 to 100, with changes in minimum enrollment of Cohort 2 and Cohort 3 from 32 and 27, respectively, to 20 in each. Updated power calculations accordingly.	To facilitate completion of the study given current enrollment challenges.

Section Numbers	Section Titles	Description of Changes	Rationale
5.1.3	Subject Exclusion Criteria	Modified exclusion criterion #3 to increase the time of allowed antibacterial therapy for the current episode of ABSSSI from 24 to 48 hours.	To minimize barriers to enrolment. This change is not expected to impact the assessment of the primary endpoint.

ADDITIONAL CHANGES FOR THIS AMENDMENT:

Section Numbers	Section Titles	Description of Changes	Rationale
1.0 5.10	Trial Summary Beginning and End of the Trial	Added text to specify the end of the study for purposes of analysis and reporting is the time when the Sponsor receives the last laboratory result or the time of final contact with the last participant, whichever comes last.	To define the end of the study for purposes of analysis and reporting.
4.3	Benefit/Risk	Updated summary of pediatric safety data as of 21-APR-2022.	To add the most recent review of safety data in children.
8.1 8.5.1	Statistical Analysis Plan Summary Efficacy Analysis Populations	Added MITT and ME populations for the analysis of exploratory efficacy endpoints.	Inadvertently not included in Protocol Amendment 6.

Section Numbers	Section Titles	Description of Changes	Rationale
8.6.1	Statistical Methods for Efficacy Analyses	Clarified that descriptive statistics will be provided for the exploratory endpoints.	To clarify the methods for reporting exploratory efficacy endpoints.
8.10	Subgroup Analyses and Effect of Baseline Factors	Subgroup analyses by treatment duration (≤8 days vs. >8 days) were added.	Since this study evaluates durations of treatment longer than the approved duration in adults, a subgroup analysis was included to evaluate the impact of longer durations on safety.
Title Page Section 10.3 Section 10.4 Section 10.7 Section 12.1 Section 12.6	Title Page Compliance with Law, Audit and Debarment Compliance with Trial Registration and Results Posting Requirements Publications Code of Conduct for Clinical Trials Microbiological Sampling and Pathogen Determination	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent a name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

Section Numbers	Section Titles	Description of Changes	Rationale
Section 5.2	Trial Treatments	The table of Trial Treatments (Table 2) was updated to add information for intervention type, dose formulation, unit dose strength, and sourcing.	To align with the Sponsor's current protocol standards.
Section 12.1	Code of Conduct for Clinical Trials	Updates to the protocol template.	To align with the current version of the Code of Conduct and other regulatory, ethical, and study governance requirements.
Global	Global	Minor formatting and editorial changes were implemented.	For clarity and consistency of the protocol text.

1.0 TRIAL SUMMARY

Abbreviated Title	Study of MK-1986 (tedizolid phosphate) in subjects from birth to <12 y with acute bacterial skin and skin structure infections (ABSSSI)
Sponsor Product Identifiers	MK-1986 Tedizolid phosphate
Trial Phase	Phase 3
Clinical Indication	Treatment of acute bacterial skin and skin structure infections (ABSSSI)
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Intravenous (IV) and/or Oral (PO). Subjects may be initiated on either IV or PO therapy, at the discretion of the investigator. Subjects initiated on IV treatment may be switched to PO 24 hours after the first dose of IV therapy when the following criteria are met: the primary skin lesion has not increased from baseline in length or width; last temperature is <37.7°C; and signs or symptoms of the primary ABSSSI site have not worsened and at least 1 has improved from baseline.
Trial Blinding	Single-blind
Treatment Groups	Treatment Group 1: Tedizolid phosphate (IV and/or PO) Treatment Group 2: Comparator (IV and/or PO) Allowed comparators are to be selected from the following, based on local clinical practice: • Allowed IV comparators: vancomycin, linezolid (outside the European Union [EU] only, as not approved for pediatric use in the EU), clindamycin, flucloxacillin, cephazolin (cefazolin); • Allowed oral comparators: linezolid (outside the EU only, as not approved for pediatric use in the EU), clindamycin, flucloxacillin, cephalexin (cefalexin). Choice of comparator should not be switched during the study, unless an IV-to-oral switch is warranted, and no oral formulation is available for the selected IV comparator. Subjects will be stratified and enrolled by age into 1 of 4 cohorts: • Cohort 1: 6 to <12 years of age; • Cohort 2: 2 to <6 years of age; • Cohort 3: 28 days to <2 years of age; or • Cohort 4: birth to <28 days of age (term and preterm* neonates). * Gestational age should be at least 26 weeks at birth Each cohort will be opened for enrollment as data become available from separate PK/safety studies.
Number of trial subjects	Approximately 100 (to ensure that at least 75 subjects receive tedizolid phosphate and are evaluable for safety and approximately 25 receive comparator) subjects will be enrolled.

Estimated duration of trial	The Sponsor estimates that the trial will require approximately 3 years from the time the first subject (or their legally acceptable representative) provides documented informed consent/assent until the last subject's last study-related contact. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.
Duration of Participation	Each subject will participate in the trial for up to 41 days from the time the subject (or their legally acceptable representative) provides documented informed consent and assent, if appropriate, through the final contact. After a screening phase of 1 day, each subject will receive assigned treatment for 6-14 days, depending on treatment assignment and whether the subject receives a treatment extension of up to 4 days. After the end of treatment, each subject will be followed through Study Day 35.
Randomization Ratio	3:1 Tedizolid phosphate: comparator

A list of abbreviations used in this document can be found in Appendix 12.10.

2.0 TRIAL DESIGN

2.1 Trial Design

In this randomized, active-controlled, parallel-group, multisite, assessor-blinded trial, tedizolid phosphate will be compared with comparator (from a specified list of allowed comparators, used in accordance with local standard of care) in subjects with acute bacterial skin and skin structure infections (ABSSSI). The trial will be conducted in conformance with Good Clinical Practice (GCP) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

Subjects from birth to less than 12 years of age with ABSSSI will be stratified and enrolled into 4 cohorts based on age:

- Cohort 1: 6 to <12 years of age;
- Cohort 2: 2 to <6 years of age;
- Cohort 3: 28 days to <2 years of age; or
- Cohort 4: birth to <28 days of age (term and preterm* neonates).

*Gestational age should be at least 26 weeks at birth.

Note: In Georgia, enrollment will be limited to subjects 3 months to <12 years (Cohorts 1, 2, and part of 3). Enrollment of subjects <3 months of age (part of Cohort 3 and all of Cohort 4) is not applicable at Georgian study sites.

Although subjects will be stratified by age group, dose level will be determined by weight. Subjects will be randomized in a 3:1 ratio to tedizolid phosphate (intravenous [IV] and/or oral suspension) or comparator (IV and/or oral dosage form). Tedizolid phosphate will be given as a once-daily, single 200-mg dose (subjects with body weight ≥50 kg) or twice-daily (q12h) 2-mg/kg doses (subjects with body weight ≥30 kg and <50 kg), or twice-daily (q12h)

2.5-mg/kg doses (subjects with body weight 3.2 kg to <30 kg). These doses have been predicted by modeling and simulation (see Section 4.2.2 for further details) to be appropriate for subjects with these body weight ranges. The dose for subjects from birth to <28 days of age will be selected based on the data from the ongoing PK study (MK-1986-014) covering this age range (see the Pediatric Study Plan in Table 1). Allowed IV comparators are: vancomycin, linezolid (outside the EU only, as not approved for pediatric use in the EU), clindamycin, flucloxacillin, and cephazolin (cefazolin). Allowed oral comparators are linezolid (outside the EU only, as not approved for pediatric use in the EU), clindamycin, flucloxacillin, and cephalexin (cefalexin).

Subjects will receive either a total of 6 to 10 days of IV and/or oral tedizolid phosphate suspension or a total of 10 to 14 days of IV and/or oral comparator. Treatment duration can be prolonged up to a maximum treatment duration of 10 days of tedizolid phosphate or 14 days of comparator, if clinically indicated based on blinded investigator assessment at Visit 4 (final day [Day 5 or 6] of dosing in the tedizolid phosphate arm) and Visit 5 (final day [Day 10 ±1 day] of dosing in the comparator arm). Subjects may be initiated on either IV or oral therapy, at the discretion of the investigator, although at least 50% of subjects in each arm must receive at least 24 hours of IV therapy. Subjects initiated on IV treatment may be switched to oral treatment 24 hours after the first dose of IV therapy, based on the criteria in Section 7.1.2.3. Details of investigator blind maintenance and criteria to consider in determining whether an extension of treatment of up to 4 days is clinically indicated are described in Section 7.1.2.4. Subjects will be followed up for efficacy and safety through the late follow-up (LFU) visit on Study Day 35.

The primary objective of the study is to use descriptive statistics to evaluate the safety of 6 to 10 days of IV and/or oral tedizolid phosphate with 10 days to 14 days of IV and/or oral comparator (or up to a maximum of 10 days of tedizolid phosphate or 14 days of comparator, if treatment is extended) in subjects from birth to <12 years of age with ABSSSI. Safety assessments will include adverse events (AEs), laboratory assessments, physical exams, including neurological assessments, and vital signs.

The secondary objective of the study is to use descriptive statistics to evaluate the investigator's assessment of clinical response in the tedizolid phosphate and comparator groups at the TOC visit on Day 25 in the ITT and clinically evaluable at TOC populations. Efficacy assessments will include lesion size measurements and investigator assessments of clinical response.

Pharmacokinetics and palatability/acceptability of the oral suspension will also be characterized in this population.

The expected sample size is approximately 100 subjects to ensure at least 75 subjects receive tedizolid phosphate and are evaluable for safety, and approximately 25 receive comparator; of these subjects, at least 36 in Cohort 1, 15 in Cohort 2, and 15 in Cohort 3 will receive tedizolid phosphate, with no minimum for Cohort 4. Based on a 3:1 randomization, this requires enrollment of approximate minima of a total of 48, 20, and 20 subjects, respectively, in the 3 oldest age cohorts. As these minima only specify that a total of 88 subjects be enrolled in Cohorts 1, 2, or 3, the remaining 12 subjects can be enrolled in any cohort. Cohorts may be capped to ensure that the minimum enrollment in each of the other cohorts

can be reached. See Section 4.2.1 for the rationale for the sample sizes in each cohort and Section 8.9 for the sample size justification.

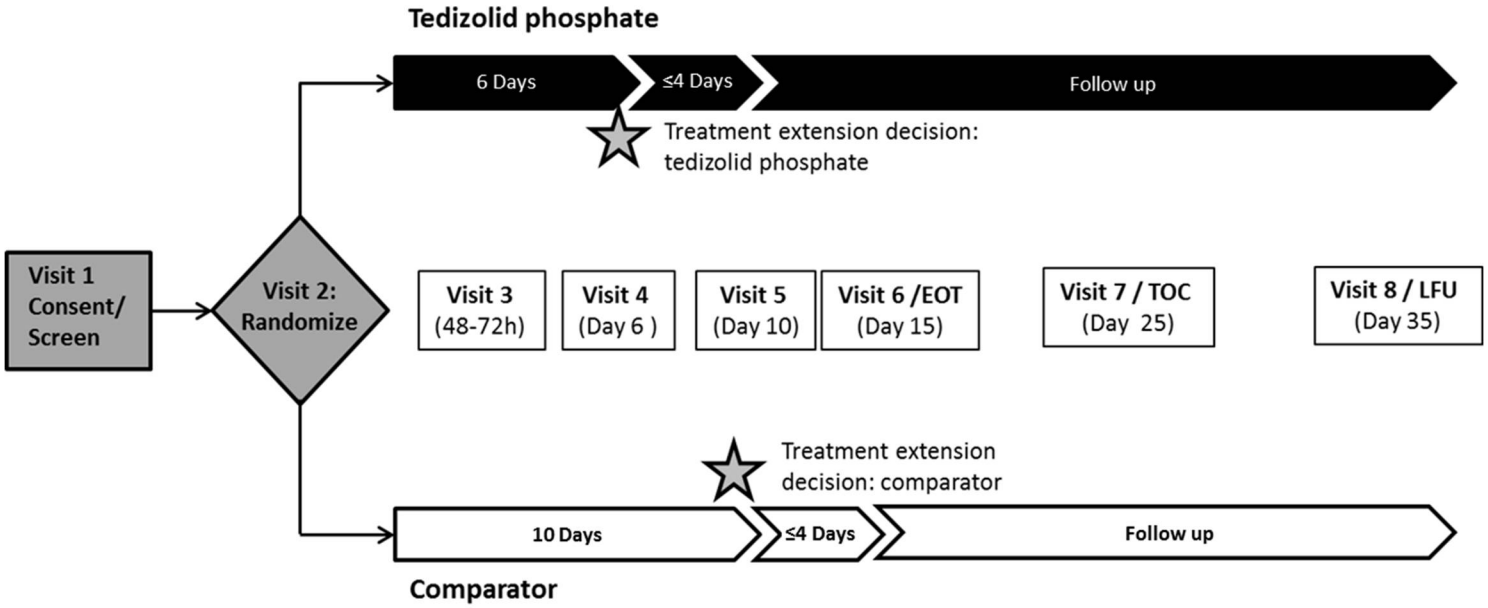
Age cohorts may enroll in parallel, but a cohort may not begin enrollment until completion of evaluation of interim PK and tolerability data from prior Phase 1 studies in the respective age cohort. In addition, a Data Monitoring Committee (DMC) will review the accruing data after the first 5 tedizolid-treated subjects in each cohort have been enrolled, to provide a recommendation on continuation (with or without dose modification) or termination.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

Figure 1 Trial Schematic



EOT=End of Therapy;

LFU=Late Follow-up;

TOC=Test-of-Cure.

Note: All study visits, including Visits 4, 5, and 6, must be performed irrespective of treatment arm or timing of EOT for a particular subject.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** The primary objective is to use descriptive statistics to evaluate the safety of IV and/or oral 6 to 10-day tedizolid phosphate with 10 to 14-day IV and/or oral comparator in subjects from birth to <12 years of age with ABSSSI. No formal hypothesis tests will be used to evaluate this endpoint.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To use descriptive statistics to evaluate investigator's assessment of clinical response in the tedizolid phosphate and comparator groups at the test-of-cure (TOC) visit on Day 25 in the intention to treat (ITT) and clinically evaluable at TOC (CE-TOC) populations.

3.3 Exploratory Objectives

(1) **Objective**: To use descriptive statistics to evaluate the programmatic early clinical response in the tedizolid phosphate and comparator groups at the 48-72 Hour Visit in subjects who remain hospitalized in the ITT population.

(2) **Objective**: To characterize the population pharmacokinetics of tedizolid in subjects from birth to <12 years of age.

(3) **Objective:** To characterize the acceptability and palatability of tedizolid phosphate oral suspension.

(4) **Objective:** To use descriptive statistics to evaluate the microbiological outcomes in the tedizolid phosphate and comparator groups at the TOC Visit in the Microbiological ITT (MITT) and Microbiologically Evaluable (ME) populations, including:

- Per-pathogen microbiological response at the TOC Visit in the MITT and ME populations
- Per-subject microbiological response at the TOC Visit in the MITT and ME populations

(5) **Objective:** To use descriptive statistics to evaluate the investigator's assessment of clinical success in the tedizolid phosphate and comparator groups at the TOC Visit in the MITT and ME populations, overall and by-pathogen.

(6) **Objective:** To describe recovery or progression of infection including changes 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), and subject reported outcome (as Wong-Baker pain score).

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) and approved labeling for detailed background information on tedizolid phosphate.

4.1.1 Pharmaceutical and Therapeutic Background

Tedizolid phosphate is an oxazolidinone prodrug antibiotic that is rapidly converted in vivo by phosphatases to the microbiologically active moiety tedizolid. Tedizolid inhibits bacterial protein synthesis by binding to the peptidyl transferase center (PTC) of the bacterial 50S ribosomal subunit. Tedizolid has bacteriostatic activity against gram-positive bacteria including common skin pathogens, *Staphylococcus aureus* (both methicillin-sensitive and methicillin-resistant strains) and *Streptococcus pyogenes*, less common species causing ABSSSI, *S. anginosus-milleri* group and *Enterococcus faecalis*, and other gram-positive aerobes and anaerobes.

4.1.2 Preclinical and Clinical Trials

4.1.2.1 Preclinical Trials in Juvenile Animals

Two pivotal repeat-dose toxicity studies were conducted in juvenile rats. Tedizolid phosphate was administered orally once daily to Sprague-Dawley and Long-Evans rats from postnatal Day 7 through 56. After oral administration of tedizolid phosphate, no effect on the reproductive system or peripheral or central nervous systems was noted. Tedizolid-related effects (which included decreased red blood cell, hematocrit, hemoglobin, platelets, and reticulocytes values) in juvenile rats were reversible and similar to effects observed in adult rats, although the effects in juvenile rats were noted at lower exposure levels compared with adult rats. These results suggest that juveniles may be more sensitive to tedizolid-related effects compared with adults.

4.1.2.2 Adult Clinical Trials

Two registrational Phase 3 studies in adult subjects with ABSSSI found 6 days treatment with 200 mg/day tedizolid phosphate to be noninferior to 10 days of treatment with 600 mg twice daily linezolid at 48 to 72 hours after the start of dosing, based on no increase in lesion area from baseline and no fever (Study TR701-112) or a 20% decrease in lesion area from baseline (Study TR701-113). Subjects in TR701-112 were required to be at least 18 years of age, while subjects in TR701-113 could be as young as 12 years of age, although only 2 adolescents were enrolled. The change in the age criteria for eligibility from the TR701-112 study to the second TR701-113 study was based on PK and safety data from TR701-111, a Phase 1 PK study in adolescents. One adolescent received tedizolid phosphate in Study TR701-113 and was considered a clinical success and experienced no treatment-emergent adverse events (TEAEs).

4.1.2.3 Pediatric Clinical Trials

Two Phase 1 studies and a single Phase 3 study have been completed in pediatric patients. In a Phase 1 Study TR701-111, 20 adolescents (aged 12 to 17 years) who were receiving prophylaxis for or had a confirmed or suspected gram-positive infection for which they were receiving concurrent antibiotics, received a single IV or oral dose of tedizolid phosphate. Results of the PK analysis showed that the mean C_{max} and $AUC_{0-\infty}$ for oral suspension or IV administration of tedizolid 200 mg were similar in adolescent and in healthy adult subjects (in adolescents, C_{max} was 16%-55% higher than and AUC was within 10% of adult values), thus the adult dose of 200 mg tedizolid phosphate was selected for continued development in adolescents. In TR701-111, TEAEs were mild, no subjects discontinued treatment due to an AE, and no deaths or SAEs were reported. Clinical laboratory evaluations, vital sign measurements, physical examinations, and electrocardiograms (ECGs) did not show clinically significant changes. A similar Phase 1, single-administration PK and safety study of oral suspension and IV tedizolid phosphate in hospitalized subjects aged 2 to <12 years (MK-1986-013; TR701-120) has also been completed. Dosing was well tolerated with no new safety findings identified.

A Phase 3 randomized assessor-blind study (MK-1986-012; TR701-122) comparing the safety and efficacy of tedizolid phosphate 200 mg once daily for 6 days versus Comparator for 10 days in adolescent subjects with complicated skin and soft tissue infections (cSSTI, also known as ABSSSI) has been completed. In Study MK-1986-012, adolescent subjects (aged 12 to <18 years) were randomized 3:1 to trial drug treatment and enrollment is complete (N=120). Allowed comparators were: IV, vancomycin, linezolid (outside of Europe only), clindamycin, flucloxacillin, and cefazolin; oral, linezolid (outside of Europe only), clindamycin, flucloxacillin, and cephalexin. The primary objective was to compare the safety of IV and/or oral 6-day 200 mg tedizolid phosphate with 10-day Comparator in adolescent in subjects with ABSSSI. The rate of clinical success was high (>93% in both the clinically evaluable and intention to treat populations) and comparable between arms. Safety was similar between arms, with a low incidence of AEs overall and no changes to the safety profile identified for tedizolid phosphate.

4.1.2.4 Ongoing Clinical Trials

One other pediatric clinical study is currently ongoing to evaluate tedizolid phosphate in the pediatric population (see also the Pediatric Study Plan in Table 1).

The Phase 1 trial, MK-1986-014 (also known as TR701-121; NCT03217565) is being conducted in pediatric subjects (birth to <2 years of age). A presentation of data from ongoing studies is included in Section 4.3 and in the IB.

4.1.3 Information on Other Trial-Related Therapy

This trial is comparator-controlled. The 5 IV and 4 oral comparators allowed for use in this trial are as follows:

- Allowed IV comparators: vancomycin, linezolid (outside the EU only), clindamycin, flucloxacillin, cephazolin (cefazolin).

- Allowed oral comparators: linezolid (outside the EU only), clindamycin, flucloxacillin, cephalexin (cefalexin).

The choice of treatments is necessary to accommodate pediatric standards of care, which can vary widely by region. In addition, aztreonam and metronidazole are allowed as concomitant medications in certain cases, as specified in Section 5.6.

The investigator should refer to the local label for information about these agents. Information about the potential risks of these comparators/allowed concomitant antibiotics will also be provided as part of the informed consent form and/or related documentation.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

As with adults, *S. aureus,* beta-hemolytic *Streptococcus* species *(S. pyogenes* and others*)*, and *Enterococcus* species are the most common pathogens in pediatric ABSSSIs. The emergence of community-acquired (CA) methicillin-resistant *S. aureus* (MRSA) is particularly troublesome in children. ABSSSIs that require hospitalization are increasing in incidence. New antimicrobials with higher potency and/or an improved toxicity profile are needed for such serious infections in children.

Tedizolid phosphate is approved for the treatment of ABSSSI in adults and adolescents 12 years of age and older in multiple regions, including the United States and EU, but its safety and effectiveness have not been established in children under 12 years of age. This study is part of a pediatric investigational program to support its global pediatric development; the overall investigational program described in Table 1 is consistent with the approved EU Pediatric Investigation Plan (PIP) and US Pediatric Study Plan (PSP).

Table 1 Pediatric Study Plan for Tedizolid Phosphate for ABSSSI

Trial	Description
Completed	
Phase 1 PK TR701-111 (NCT01156077)	Open-label, multicenter, two-part, single-dose, parallel design, safety, and PK study of oral and IV TR-701 FA in subjects 12 to 17 years
MK-1986-012 (TR701-122) (NCT02276482)	Phase 3 study of IV-to-oral 6-day tedizolid phosphate compared with 10-day comparator in subjects 12 to <18 years with ABSSSI; study has been completed.
MK-1986-013 (TR701-120) (NCT02750761)	Phase 1, single-dose safety and PK study of oral and IV tedizolid phosphate in hospitalized subjects 2 to <12 years of age

Trial	Description
Ongoing or planned	
MK-1986-018 (TR701-128) (NCT03176134)	Randomized, assessor-blind, safety and efficacy study of IV or oral tedizolid phosphate and comparator for ABSSSI in subjects from birth* to <12 years
MK-1986-014 (TR701-121) (NCT03217565)	Phase 1, single and multiple-dose safety and PK study of oral and IV tedizolid phosphate in hospitalized subjects under 2 years of age*

ABSSSI=acute bacterial skin and skin structure infections; FA=free acid; IV=intravenous; PK=pharmacokinetic(s)

* Including both preterm and term neonates.

Pediatric experience with tedizolid phosphate is largely limited to results from the completed TR-701-111 and MK-1986-012 studies, both of which included subjects 12 to <18 years of age; and MK-1986-013, a single-dose safety and PK study in subjects 2 to <12 years of age. Tedizolid phosphate has not been studied in subjects <12 years of age with ABSSSI; therefore, the primary endpoint is to assess the safety of tedizolid phosphate in this population. The trial design is not powered for inferential statistics, and efficacy is not a primary endpoint.

The sample size of 100 subjects is divided among 4 age cohorts in this study, as described in Section 2.1. The minimum sample size required in each cohort declines with age to minimize the numbers of subjects in the youngest age cohorts while providing a sufficient number of subjects to assess whether there are common AEs leading to intolerability in each age cohort (see also Section 8.9). No minimum enrollment is required in the youngest age cohort, although subjects with identified cases in the neonatal population are also targeted for enrollment. This is due to the expected rarity of ABSSSI in the neonatal population. In an evaluation of data from the Intermountain Healthcare System (which covers >95% of infants ≤3 months in Utah), only 172 cases of skin and soft tissue infection (SSTI) were identified from 2004 to 2011 in infants ≤3 months of age (approximately 0.46 cases per 1,000 births) [1].

4.2.2 Rationale for Dose Selection/Regimen/Modification

Results of TR701-111 in 20 adolescent subjects established that exposure was similar in adults and adolescents and that tedizolid phosphate was well tolerated with no clinically significant safety findings. These PK data confirmed that no adjustment from the adult dose (200 mg once daily) was needed in adolescents. These data were also used to estimate the PK in subjects from 2 to 12 years of age via allometric scaling, modeling, and simulation.

Prior to initiation of study MK-1986-018, study MK-1986-013, a single-dose PK study in children 2 to <12 years of age, was initiated to provide data to support dose selection in children 2 to <12 years of age. Following a pair of interim analyses of study MK-1986-013, the dosing scheme was updated in MK-1986-018. The goal of these interim analyses was to identify a dose that approximated exposure in adults. Of particular interest was the area under

the curve, as AUC/MIC is the parameter most closely related to efficacy, for oxazolidinones, but C_{max} was also considered, to ensure that the C_{max} distribution was largely within adult experience. The results of these interim analyses suggested that, for children 16 kg and larger, the total daily dose should be 6 mg/kg daily up to a maximum of 200 mg/day; however, for children under 40 kg body weight, this should be given as a split dose, 3 mg/kg twice daily, to maintain a C_{max} distribution in line with prior experience in adults and/or adolescents. This dosing scheme was initially selected for the oldest (6 to <12 years) age group in study MK-1986-018.

Since that time, however, complete results from MK-1986-013 and MK-1986-012, a safety and efficacy study in adolescents 12 to <18 years of age, as well as interim results from study MK-1986-014, a PK and safety study in children birth to <2 years of age, have become available. Modeling and simulation were repeated using these additional data, and results indicated that the dose for children under 12 years of age should be adjusted to provide a closer match to adult PK. Another interim analysis was conducted following completion of enrollment of the 28 day to <2 year age group (N=14) in study MK-1986-014, which supported the same dosing schedule in children 28 days to <2 years of age, and therefore the corresponding weight minimum for this dose schedule has been adjusted downward to 3.2 kg (the fifth percentile weight of a 28 day old infant).

Dosing of children 3.2 kg and higher (Groups 1, 2 and 3) in study MK-1986-018 has therefore been adjusted as follows:

- Children 50 kg and higher will receive 200 mg once daily;
- Children 30 to <50 kg will receive 2 mg/kg, twice daily; and
- Children 3.2 to <30 kg will receive 2.5 mg/kg twice daily.

The revised dose is based on weight even though subjects are stratified by age. These dose levels are predicted to produce an AUC distribution similar to adults, with a percent target attainment well over 95% at the breakpoint MIC (0.5 mg/L), while maintaining a C_{max} distribution similar to adults and/or adolescents.

Further data from study MK-1986-014, a single- and multiple (amendment 04) dose PK and safety study in children <2 years of age, will support dose selection for neonatal subjects <28 days of age in this study. Final selection of a dose level for neonates <28 days of age will be added once additional data have been analyzed from study MK-1986-014. During this study, a DMC will also review the accruing data, after the first approximately 5 tedizolid-treated subjects in each cohort have been enrolled, to provide a recommendation on continuation (with or without dose modification) or termination.

With respect to the duration of therapy, discussion with pediatricians and regulators has revealed a strong tendency within the pediatric medical community to use longer durations of antibiotic therapy for children, and a general lack of comfort with restricting antibiotic duration without the *option* to treat longer. For this reason, if a subject is deemed to be responding to therapy yet not responding rapidly enough to allow a level of comfort in stopping therapy at 6 days (for tedizolid phosphate) or 10 days (for comparator), an extension of therapy of up to 4 days is allowed. This assessment will be made in a blinded fashion at Visit 4 and Visit 5, as described in Section 7.1.2.4.

4.2.2.1 Rationale for the Use of Comparators

Subjects will be randomized to study drug or comparator to have a controlled comparison of the safety and effectiveness of tedizolid phosphate in subjects from birth to <12 years of age. Since the ABSSSI condition requires antibiotic treatment, the trial has an active control group. To standardize control group treatment, a list of permitted comparators is provided in Section 4.1.3. This list of comparators is in accordance with the PIP/PSP agreed with the EMA and FDA. Recommendations of comparators and doses are provided in Table 2. Investigators must thoroughly review potential contraindication, including hypersensitivity, to the comparator; risk and benefit must be fully assessed prior to assigning the comparator.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The trial design, as agreed with the FDA and EMA, is not powered for inferential statistics, and, thus, efficacy is not a primary endpoint. The secondary efficacy endpoint is the investigator's assessment of clinical response in the tedizolid phosphate and comparator groups at the TOC Visit (22 to 29 days). Programmatic early clinical response in the tedizolid phosphate and comparator groups at the 48- to 72-hour visit will also be evaluated as an exploratory endpoint, in subjects who remain hospitalized at that visit.

The investigator's assessment of clinical response at TOC is a secondary endpoint in the PIP, in accordance with EMA guidance. Clinical response is defined by ALL of the following:

- resolution or near-resolution of most disease-specific signs and symptoms; AND
- absence or near-resolution of regional and systemic signs of infection; AND
- no new signs, symptoms, or complications attributed to the infection under study (thus no further antibiotic treatment is required for the primary lesion).

By contrast, failure is defined by any of the following:

- requires additional antibiotic therapy for treatment of the primary lesion; *or*
- requires unplanned major surgical intervention (eg, amputation) due to failure of the study drug; *or*
- develops osteomyelitis after baseline; *or*
- develops persistent gram-positive bacteremia; *or*
- develops TEAE/death requiring discontinuation.

Subjects are treated as indeterminate if they have conditions that prevent meaningful assessment of efficacy (ie, missing data due to subject lost to follow-up or withdrawal of consent, cellulitis or abscess infected/coinfected with a gram-negative organism, wound infection that has a gram-negative coinfection that cannot be treated with metronidazole or aztreonam, or osteomyelitis present at baseline).

See Table 4 for the full definitions of success, failure and indeterminate. These definitions match those in prior adult studies, and clinical outcome at TOC, 7 to 14 days after the end of

treatment, remains the EMA-preferred endpoint for evaluation of medicinal products indicated for treatment of ABSSSI [2].

The programmatic early clinical response at the 48- to 72-hour visit (a responder is defined as a subject with at least a 20% reduction in lesion surface area) is the FDA-recommended endpoint for primary assessment of efficacy [3]. However, this guidance is focused on ABSSSI assessment in adults. For children, particularly infants and small children, the utility of a 20% reduction criterion in predicting outcome is unclear. Therefore, this study will investigate this criterion as an exploratory endpoint, as well as the concordance between programmatic early clinical response and the investigator assessment of clinical response at TOC.

To characterize the microbiological response of tedizolid phosphate and comparator groups in subjects with pathogens cultured at baseline, microbiological outcomes will be assessed programmatically using microbiological data from samples obtained at the TOC Visit (both by-subject and by-pathogen).

Detailed definitions of the secondary efficacy endpoint (including planned analyses populations) are provided in Section 8.0.

4.2.3.2 Safety Endpoints

The primary endpoint is to assess the safety of tedizolid phosphate in the pediatric population. Multiple assessments are conducted to establish the safety profile, including AEs, vital signs, physical exams, including specific neurological and visual acuity assessments, and hematology and clinical chemistry. While most of these are standard safety assessments for most therapeutic agents, neurological and visual acuity examinations are included to assess any potential risk for optic or peripheral neuropathy, which has been reported in prior experience with prolonged use of linezolid, a compound in the same chemical class as tedizolid phosphate (oxazolidinones). Peripheral or optic neuropathy has not been identified for tedizolid phosphate in prior clinical experience in adults in treatment for ABSSSI. Other potential risks to be evaluated in this study include hematologic adverse effects (decreases in hemoglobin, platelets, and/or WBC counts) and lactic acidosis, which are both associated with higher doses and/or longer durations of exposure to another oxazolidinone. These will be evaluated by hematology and chemistry laboratory assessments, respectively. A list of specific safety analyses is provided in Section 8.0, with their timing set out in the Trial Flow Chart in Section 6.0.

4.2.3.3 Pharmacokinetic Endpoints

PK endpoints will be evaluated to characterize the population PK of tedizolid in subjects from birth to <12 years of age, as described in Section 7.1.3.2. These analyses will be reported separately.

4.2.3.4 Pharmacodynamic Endpoints

PK/PD analyses will be performed to determine probabilities of clinical success, microbiological response, and safety outcomes based on individual metrics of tedizolid exposure. These analyses will be reported separately.

4.3 Benefit/Risk

A persistent, growing, and unmet medical need exists for new, effective antibiotic medications that provide a significant therapeutic and safety advancement over those currently in use. CA-MRSA has become one of the most common causes of ABSSSI in both children and adults in the past 15 years [4] [5], particularly in the United States. New antimicrobials with higher potency are needed for such serious infections, especially given the rising incidence of highly resistant and virulent pathogens such as MRSA and vancomycin-intermediate and -resistant *S. aureus*. The limited or unproven activity and the toxicity profile of currently available antibiotics indicated for the treatment of ABSSSI contribute to the challenges of treating these infections.

Tedizolid phosphate was studied in a pair of Phase 3 trials that included 1333 adults with ABSSSI who received treatment with either tedizolid phosphate or linezolid. Tedizolid phosphate was statistically noninferior to linezolid for the primary efficacy analyses of early clinical response (>20% reduction in lesion size at 48 to 72 hours Visit), and positive results were shown for secondary analyses at the end of treatment (EOT) Visit, and for Investigator assessment of clinical response at 7 to 14 days after the end of therapy. Tedizolid phosphate was generally well tolerated; 42.7% of tedizolid phosphate subjects experienced at least 1 TEAE (similar to the incidence for the comparator, 43.2%). Gastrointestinal AEs (nausea, diarrhea, and vomiting) and headache were the most commonly reported TEAE; incidence of GI AEs was higher in linezolid patients. Less than 1% of subjects in each treatment group discontinued trial drug due to an AE and approximately 2% of subjects in each treatment group experienced an SAE.

Hematological parameter values were carefully monitored, since myelosuppression has been reported for linezolid. Overall, mean values of ANC, hemoglobin values, and platelet counts remained generally stable over the course of the studies. In the Phase 3 adult trials, clinically significant changes in neutrophil and hemoglobin were generally similar for both treatment arms, but fewer subjects had substantially abnormal platelet values in the tedizolid arm than in the linezolid arm. Likewise, the incidences of ANC, platelet, and hemoglobin values below the lower limit of normal were lower in the tedizolid arm. No suggestion of myelosuppression was observed in the Phase 3 study in adolescents with ABSSSI (MK-1986-012). Phase 1 studies conducted in healthy adults exposed to tedizolid phosphate for 21 days showed a possible dose and duration effect on hematologic parameter values beyond 6 days of treatment. See the IB for additional details.

As of 21-APR-2022, 242 pediatric subjects <18 years of age have been dosed with single or multiple doses of tedizolid phosphate, including 130 children <12 years of age. The results of completed studies, described in Section 4.1.2 as well as in the IB, have indicated that tedizolid phosphate has been well tolerated in adolescents receiving single or multiple 200 mg doses.

As of 21-APR-2022, 69 subjects from birth to <12 years of age, with an underlying known or suspected gram-positive infection or receiving prophylaxis for infection, have received a single oral or IV dose of tedizolid phosphate. These data include 16 subjects 6 to <12 and 16 subjects 2 to <6 years of age in the (completed) study MK-1986-013, and 14 subjects 28 days to <2 years, 12 full term neonates <28 days of age, and 11 pre-term neonates <28 days of age in the ongoing study MK-1986-014. Dosing has been generally well

tolerated across these age groups, with a low proportion of subjects reporting AEs (15; 21.7%) across the age groups with no discernable trends with respect to age, dose, or route. Four AEs (5.8%; comprising increased immature granulocytes, anemia, hemoglobin decreased, and nausea) were considered drug related. For the related non-serious AEs of anemia and hemoglobin decreased, an underlying surgical intervention may have contributed or caused the events. There have been 2 SAEs (2.9%), neither of which have been considered drug related ("therapeutic product effect incomplete" with respect to the subject's response to their concomitant antibiotic and failure of medical management of underlying appendicitis), both of which resolved. Review of safety labs and vital signs has not suggested a safety signal or indicated a change to the safety profile observed in adults or adolescents.

As of the most recent interim analysis in MK-1986-018 (data cutoff 08-MAR-2022, including all subjects enrolled through 06-JAN-2022), 55 subjects from 28 days to <12 years of age, with underlying acute bacterial skin and skin structure infection, have received multiple IV and/or oral tedizolid phosphate for 6 to 10 days and completed the follow-up period for safety. These data include 40 subjects 6 to <12, 14 subjects 2 to <6, and 1 subject 28 days to <2 years of age randomized to tedizolid phosphate. Dosing has been generally well tolerated across these age groups, with few subjects reporting AEs (12; 21.8%) across the age groups with no trends with respect to age, dose, or route and no SAEs. The most common observed AEs were nausea (3, 5.5%), phlebitis (3, 5.5%), and allergic rhinitis (2, 3.6%). Review of safety labs and vital signs has not suggested a safety signal or indicated a change to the safety profile observed in adults or adolescents. An additional 6 subjects were randomized to tedizolid phosphate between this interim analysis and the cutoff point of 21-APR-2022, including 4 subjects 6 to <12 years of age, 1 subject 2 to <6 years of age, and 1 subject 28 days to <2 years of age. These subjects have likewise shown good tolerability of the medication, with only 1 having AEs, none of which were serious or considered related to study medication. Overall, across the pediatric program, there has been no change to the safety profile as compared to adults, and no indication of a change in safety profile with age.

Unlike linezolid, tedizolid phosphate was not shown to be a monoamine oxidase (MAO) inhibitor *in vivo* and is therefore unlikely to increase the risk of serotonin syndrome. While tedizolid was a weak MAO inhibitor in vitro, exposure to tedizolid as a result of tedizolid phosphate administration does not produce functionally significant MAO inhibition in the central nervous system. However, the potential risk for serotonin syndrome has not been evaluated in Phase 2 and 3 clinical trials, as subjects taking MAO inhibitors and serotonergic medications were excluded.

Peripheral and optic neuropathies have been described in patients treated with linezolid for longer than 28 days. A 9-month study of rat neurotoxicity did not show evidence of optic or peripheral nerve toxicity at exposures approximately 8-fold greater than anticipated human clinical oral exposure at the recommended dose of tedizolid phosphate. A clinical study evaluating ophthalmologic and neurological effects in healthy adults treated with the therapeutic dose of tedizolid phosphate for 10 days was negative for findings of optic or peripheral neuropathy. In Phase 3 trials, reported adverse reactions for peripheral neuropathy and optic nerve disorders were infrequent and similar between treatment arms (peripheral neuropathy 1.2% vs 0.6% and optic nerve disorders 0.3% vs 0.2%, for tedizolid phosphate vs linezolid, respectively). The safety and efficacy data generated so far support a positive risk:benefit balance for the use of tedizolid phosphate in the current and future evolving

environment of microbial resistance in ABSSSI. Tedizolid phosphate addresses the distinct areas of unmet medical need and has the potential to provide a significant improvement in the treatment of ABSSSI compared to currently marketed products. It is associated with high success rates and similar or more favorable safety characteristics compared with linezolid for the treatment of ABSSSI. In addition, tedizolid phosphate is convenient to use based on the short course of therapy, no dose adjustment between oral tablet and IV administration, and a uniform dosage regimen for all patient populations. The reduced treatment period tested in adults for tedizolid phosphate compared to that for linezolid is expected to decrease the length of hospitalizations, which is a particularly important factor to pediatric patients and their families.

Microbiologically and pharmacologically, tedizolid phosphate offers many benefits over other available antibiotics. In vitro studies suggest that tedizolid phosphate has a low propensity for resistance development against key pathogens involved in ABSSSI. Tedizolid phosphate has no known antagonism or synergy with other commonly used antibacterial agents. Furthermore, tedizolid phosphate is not associated with clinically relevant drug-drug interactions with drugs such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and vasoconstrictors, and is not adversely affected by metabolism or interactions with the cytochrome P450 enzyme system. Orally administered tedizolid phosphate can result in inhibition of breast cancer resistance protein (BCRP) at the intestinal level, increasing plasma concentrations of BCRP substrates, and the potential for adverse reactions. If possible, an interruption in the treatment of the co-administered BCRP substrate medicinal product should be considered during treatment with oral tedizolid phosphate, especially for BCRP substrates with a narrow therapeutic index (eg, methotrexate, topotecan, irinotecan, or rosuvastatin).

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and informed consent documents. Although potentially more frequent than the standard of care, the planned study procedures (see Section 6.0 – Trial Flow Chart) are generally typical procedures performed for this subject population. Trial procedures, including the number of blood draws for PK sampling, are limited in order to minimize risk. Additional burden may be incurred due to visits after release from the hospital; however, the procedures performed at these visits are generally not likely to lead to significant harm (e.g, blood draws, urine collection, physical examinations, and vital signs) and are necessary to support a robust evaluation of the safety and efficacy of the investigational drug. Information regarding the specific benefits and risks of comparator treatments in the study may be found in the local product labels for each comparator.

Based on the assessment of postmarketing adverse drug experiences reported to date, no significant new information regarding the safety of tedizolid phosphate has been established. The safety data received to date for tedizolid phosphate remains consistent with the current product labeling.

In summary, these potential risks listed for tedizolid phosphate have not been observed in clinical experience at the therapeutic dose and durations planned for this study, so the level of risk is considered to be very low. The benefit:risk profile of tedizolid phosphate is thus considered to be positive.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects from birth to less than 12 years of age with ABSSSI requiring antibiotic therapy and caused by suspected or documented gram-positive pathogen(s) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have a parent/legally acceptable representative (LAR) who is able to give documented informed consent and willing and able to comply with all required study procedures. Assent is required of subjects who in the investigator's judgment are capable of understanding the nature of the study.
2. Be male or female from birth to <12 years of age at the time of consent. Preterm neonates should have a gestational age of at least 26 weeks at birth.

   Note: In Georgia, enrollment age of a male or female subject is limited to 3 months to <12 years (Cohorts 1, 2, and part of 3). Subjects <3 months old (part of Cohort 3 and all of Cohort 4) are not permitted to enroll into the study at Georgia sites.
3. Have adequate venous access for collection of protocol-specified samples and administration of study drug (for subjects receiving IV study medication)
4. Have ABSSSI, defined by meeting the definition of at least 1 of the following 3 clinical syndromes:

   a. Cellulitis/erysipelas defined as a diffuse skin infection, characterized by all of the following:

      - Spreading area of erythema, edema, and/or induration (EEI); EEI should extend at least 4 cm in 1 dimension for subjects 4 years and older
      - 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 ≥38°C (100.4°F) oral or ≥38.4°C (101.1°F) tympanic or rectal (observed by a health care provider)
  - WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
  - >10% immature neutrophils
  - Patient-reported pain of at least 6 (Wong-Baker pain scale) or, for nonverbal subjects, a pain score of at least 4 (FLACC behavioral pain scale)

b. Major cutaneous abscess, defined as an infection characterized by a collection of pus apparent upon visual examination within the dermis or deeper that is accompanied by all of the following:

- Erythema, edema and/or induration (EEI); EEI should extend at least 4 cm in 1 dimension for subjects 4 years and older
- 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 radiological 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 ≥38°C (100.4°F) oral or ≥38.4°C (101.1°F) tympanic or rectal (observed by a health care provider)

- WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
- >10% immature neutrophils
- Patient-reported pain of at least 6 (Wong-Baker pain scale) or for nonverbal subjects, a pain score of at least 4 (FLACC behavioral pain scale)

c. Wound infection, defined as an infection characterized by purulent drainage from a wound with surrounding EEI; and is 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
  - Is associated with an original surgical incision ≥1 cm
  - Involves purulent drainage (spontaneous or therapeutic) with surrounding EEI; EEI should extend extending at least 4 cm in 1 dimension for subjects 4 years and older.
- Or, posttraumatic wound (including penetrating trauma) characterized by purulent drainage (spontaneous or therapeutic) with surrounding EEI; EEI should extend at least 4 cm in 1 dimension for subjects 4 years and older
- 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 ≥38°C (100.4°F) oral or ≥38.4°C (101.1°F) tympanic or rectal (observed by a health care provider)
  - WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
  - >10% immature neutrophils
  - Patient-reported pain of at least 6 (Wong-Baker pain scale) or for nonverbal subjects, a pain score of at least 4 (FLACC behavioral pain scale)

5. Have local symptoms of ABSSSI that started within 14 days before Study Day -1.

6. Have a suspected or documented gram-positive infection from baseline Gram stain or culture (see Appendix 12.6). 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. Note: 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.
7. Have body weight ≥3.2 kg for children from 28 days to <12 years old; for children under 28 days old, weight eligibility criterion will be updated in future amendment.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has an uncomplicated skin and skin structure infection such as furuncles, minor abscesses (area 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. Has ABSSSI 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 and available, as described in Section 5.6, may be enrolled if they meet the other eligibility criteria.
    - Perianal abscess
    - Infection within the mouth and/or perioral structures or within the hairline (if this limits measurement of lesion size)
    - Atopic dermatitis, eczema, and psoriasis
    - Infections associated with, or in close proximity to, a prosthetic device
    - Concomitant severe acute infection at another site not including a secondary ABSSSI lesion (eg, septic arthritis, endocarditis, osteomyelitis)
    - Infected burns
    - Any evolving necrotizing process involving deep soft tissue structures (ie, necrotizing fasciitis, pyomyositis, omphalitis)
    - Infected human or animal bites (insect bite-related infections are permitted)
    - Infections at vascular catheter sites or involving thrombophlebitis
    - Incision surgical site infection 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. Has received antibacterial therapy for treatment of the current episode of ABSSSI unless:
   - ≤48 hours of effective antibacterial drug therapy with a short-acting antibacterial drug (defined as administration frequency of 1 or more doses per 24 hours)

   OR

   - Response to prior antibacterial therapy for the primary infection site of ABSSSI is considered by the investigator to be failure (no improvement in signs and symptoms [eg, fever, pain, tenderness, lesion size increase]) after at least 48 hours of therapy
4. Has known bacteremia, severe sepsis, or septic shock at the Screening Visit
5. Has significant or life-threatening condition, disease, or organ system condition (eg, endocarditis, meningitis)
6. Has recent history of opportunistic infections where the underlying cause of these infections is still active (eg, leukemia, transplant, acquired immunodeficiency syndrome), or is suspected to be at risk of opportunistic infections or infection with unusual pathogens (eg, primary immune deficiency, cystic fibrosis)
7. Has received or is receiving treatment for active tuberculosis (within 1 month)**
8. Has known or suspected severe neutropenia (absolute neutrophil count [ANC] <1000 cells/mm^3)
9. Is human immunodeficiency virus (HIV) positive and has known or suspected CD4 cell count <15%. Note: HIV Testing is not required for eligibility.
10. Has renal impairment that requires peritoneal dialysis, plasmapheresis, hemodialysis, venovenous dialysis, or other forms of renal filtration
11. Has known or suspected severe hepatic impairment
12. Has 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. For neonates, an ECG is not required, but ECG data will be collected if available.
13. Has received investigational medicinal product within 30 days before the first administration of study drug. (Investigational product, in this case, refers to a product that is not approved in the country in which the subject is enrolled, for either adults or children, for any indication.)**

14. Has an investigational device present or removed within 30 days before the first administration of study drug or presence of device-related infection
15. Was previously treated in tedizolid phosphate clinical studies (including this protocol)**
16. Has contraindication, including hypersensitivity, to tedizolid phosphate, other oxazolidinones, or any component in the formulation
17. Has contraindication, including hypersensitivity, to all available comparator drugs. Contraindication to one comparator does not preclude participation if an alternative comparator can be used.
18. Has a wound infection, and meets either of the following:
    - History of hypersensitivity to ceftazidime, aztreonam, or any component of the aztreonam formulation, if aztreonam adjunctive therapy is required, or
    - History of hypersensitivity to metronidazole or any component of the metronidazole formulation, if metronidazole adjunctive therapy is required
19. Needs oral administration of methotrexate, topotecan, irinotecan, or rosuvastatin, during administration of oral study drug (administration during the follow-up period, ie, after the EOT Visit, is allowed, as is administration during treatment with IV study drug).**
20. Is a female who is pregnant or nursing, or who is of childbearing potential and not abstinent; or a male who is not abstinent.
21. Has circumstances, including those of parent(s)/legal guardian(s), that make adherence to the protocol, compliance with study drug administration, or completion of the study unlikely.
22. Is or has an immediate family member (e.g., spouse, parent/legal guardian, or sibling) who is investigational site or sponsor staff directly involved with this trial.
23. Uses 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 (refer to Appendix 12.9)**
24. Is identified as having used illicit drug(s) (urine drug screening not required for entry).**

****Note: Breastfed subjects should be excluded if the mother is receiving these excluded medications.**

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 2.

Subjects may be initiated with either oral or IV treatment, at the discretion of the investigator, although at least 50% of subjects in each arm should receive at least 24 hours of IV therapy. Subjects initiated on IV therapy can be transitioned to oral therapy 24 hours after the first IV dose, if they meet the criteria in Section 7.1.2.3.

Table 2 Trial Treatments

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Tedizolid phosphate	Experimental	Tedizolid Phosphate	Drug	IV/oral suspension	IV: Refer to product labeling Oral: 20 mg/mL	200 mg	IV or oral	Once-daily, single 200-mg dose (subjects with body weight ≥50 kg), for 6 to 10 days	Test Product	IMP	Central
Tedizolid phosphate	Experimental	Tedizolid phosphate	Drug	IV/oral suspension	IV: Refer to product labeling Oral: 20 mg/mL	2 mg/kg	IV or oral	Twice-daily (q12h) 2-mg/kg doses (subjects with body weight ≥30 to <50 kg), for 6 to 10 days	Test Product	IMP	Central
Tedizolid phosphate	Experimental	Tedizolid phosphate	Drug	IV/oral suspension	IV: Refer to product labeling Oral: 20 mg/mL	2.5 mg/kg	IV or oral	Twice-daily (q12h) 2.5-mg/kg doses (subjects with body weight ≥3.2 to <30 kg), for 6 to 10 days	Test Product	IMP	Central
Comparator	Active Comparator	Vancomycin	Drug	IV	Refer to product labeling	10 mg/kg with goal trough level of 10 to 15 mcg/mL	IV	Every 6 to 8 hours, for 10 to 14 days	Comparator	IMP	Local or central where necessary

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Comparator	Active Comparator	Cephazolin (Cefazolin)	Drug	IV	Refer to product labeling	50 or 100 mg/kg/day (up to 1,000 mg/dose)	IV	Every 6 to 8 hours, for 10 to 14 days	Comparator	IMP	Local or central where necessary
Comparator	Active Comparator	Linezolid	Drug	IV/oral suspension	Refer to product labeling	10 mg/kg/dose (up to maximum dose 600 mg)	IV or oral	Every 6 to 8 hours, for 10 to 14 days	Comparator	IMP	Local or central where necessary
Comparator	Active Comparator	Clindamycin	Drug	IV/oral suspension	Refer to product labeling	IV: 30 mg/kg/day (up to 600 mg/dose) Oral: 30 mg/kg/day (up to 450 mg/dose)	IV or oral	3 times daily, for 10 to 14 days	Comparator	IMP	Local or central where necessary
Comparator	Active Comparator	Flucloxacillin	Drug	IV/oral suspension	Refer to product labeling	IV: 125 to 250 mg (2 to 10 years) or 62.5 to 125 mg (<2 years) Oral: 125 mg (2 to 10 years) or 62.5 mg (<2 years)	IV or oral	Every 6 hours, for 10 to 14 days	Comparator	IMP	Local or central where necessary
Comparator	Active Comparator	Cephalexin (Cefalexin)	Drug	Oral suspension	Refer to product labeling	25 to 50 mg/kg/day (up to 500 mg/dose)	Oral	Every 6 to 12 hours, for 10 to 14 days	Comparator	IMP	Local or central where necessary

EEA =European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; q12h=twice daily.
The classification of IMP and NIMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.
For comparators, doses should be based on the recommendations provided above. If the local standard of care differs from dosages provided in this table, sites may dose comparators according to the local standard of care. Switches between comparator antibiotics are not allowed for a given subject except when the subject is to be switched to oral treatment and there is no oral option for a selected IV initial antibiotic (eg, subject is initiated on vancomycin and needs to be transitioned to oral comparator).

Trial treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the subject is allocated/assigned.

All supplies indicated in Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

In subjects 28 days to <12 years of age, tedizolid phosphate (IV and/or oral) will be dosed as follows:

- Subjects ≥ 50 kg body weight, 200 mg once daily
- Subjects 30 to <50 kg, 2 mg/kg twice daily (q12h)
- Subjects 3.2 to <30 kg, 2.5 mg/kg twice daily (q12h)

In subjects from birth to <28 days of age, the dose will be added, by amendment, once confirmed (see Section 4.2.2).

The maximum tedizolid phosphate dose is 200 mg daily for any subject regardless of weight. Instructions for preparation of the IV or oral suspensions and dosing tables by weight are provided in the pharmacy manual.

Note: Only baseline body weight should be used to select tedizolid phosphate dosage (both IV and oral) for the entire trial.

Comparator drug (IV and/or oral) will be dosed according to the recommended dosages in Table 2. If the local standard of care substantially differs from dosages in Table 2, sites may dose comparators according to the local standard of care.

Note: The decision to give study drug by the IV and/or oral route is at the discretion of the investigator. At least 50% of subjects in each arm must receive at least 24 hours of IV therapy. For subjects initiated on IV study drug, oral switch is permitted after 24 hours on IV, if subjects meet the IV-to-oral switch criteria in Section 7.1.2.3.

5.2.2 Timing of Dose Administration

Tedizolid phosphate is given once daily (subjects with body weight ≥50 kg) or twice daily (subjects with body weight ≥3.2 kg and <50 kg), with or without food. The twice-daily

dosages should be 12 hours apart during the study. There is a 12±2 hour time window for dosing to minimize disruption to subjects' rest schedules.

Comparators will be dosed according to recommendations provided in Table 2 or local standard of care, if the recommended dosing is different from local guidelines.

When IV study drug is administered, no other IV therapy should be administered concurrently.

Subjects who vomit after oral dosing should not receive an immediate "make-up" dose but should continue to the next dose in accordance with the dosing schedule.

5.2.3 Trial Blinding

A single-blinding technique will be used. A blinded assessor(s) at the site will not know the treatment assignment administered, however the unblinded investigator(s), unblinded site staff, subject, and Sponsor personnel will be aware of the group assignments.

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT). There are 2 treatment arms. Subjects will be assigned randomly in a 3:1 ratio to tedizolid phosphate or comparator, respectively. A total of approximately 100 subjects will be enrolled in the study, including at least 75 subjects who will receive tedizolid phosphate and approximately 25 subjects who will receive comparator. See Section 2.1 for the planned minimum number of subjects to be enrolled and receive tedizolid phosphate in each age cohort.

5.4 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. Age; subjects will be stratified and enrolled into one of 4 cohorts by age:
    - Cohort 1: 6 to <12 years
    - Cohort 2: 2 to <6 years
    - Cohort 3: 28 days to <2 years
    - Cohort 4: birth to <28 days (term and preterm neonates)

5.5 Concomitant Medications/Vaccinations (Allowed and Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Restrictions for prior or concomitant therapy are listed in Table 3.

Table 3 Concomitant Therapy Rules

Category	Medications and Procedures	Comments on Use[a]
Allowed	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.
Prohibited[b]	For subject receiving oral study medication, oral topotecan, irinotecan, rosuvastatin, or methotrexate	Prohibited through EOT Visit
	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 ABSSSI, such antibiotic therapy should not have overlapping antibacterial activity with the study drug for the pathogen isolated from the ABSSSI lesion at baseline, if possible.	Prohibited through the LFU Visit; prior therapy must be short acting (administration frequency is 1 or more doses per 24 hours), with exception of ≤24 hours prophylactic therapy prior to surgery during the study. Antibiotics without activity against ABSSSI pathogens or those with local activity are allowed.
	Monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin 5-hydroxytryptamine receptor agonists (triptans) and buspirone	Refer to Appendix 12.9 for examples. Prohibited from 14 days prior to study through the EOT Visit.
	Topical heavy metal extracts such as lead subacetate and mercurial chrome.	Prohibited from Screening through the EOT Visit.

ABSSSI=acute bacterial skin and skin structure infections; EOT=end of therapy; LFU=late follow-up

a Refer to Section 5.1.3 for details on exclusion criteria

b For breastfed subjects, consideration should be given to any prohibited medications taken by the mother, with appropriate steps taken to avoid exposure to the subject. See also Section 5.1.3.

5.6 Rescue Medications & Supportive Care

No rescue medications are specified to be used in this trial. However, if there is no clinical improvement, the investigator should discontinue the subject from the study, and switch the subject to other therapy based on local standard practice.

In countries and/or sites where aztreonam is available, concomitant 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 wound 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 but continue in the trial to complete assessments, as specified in Section 7.1.4.1.

In countries and/or sites where aztreonam is not available, concomitant antibiotics for gram-negative aerobic or anaerobic pathogens in wound infections are not permitted and the subject(s) would be excluded from participating in the trial.

5.7 Diet/Activity/Other Considerations

There are no dietary or activity restrictions for subjects receiving tedizolid phosphate.

The specific comparator's label instructions should be followed for subjects receiving a comparator.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.2 – Discontinued Subjects Continuing to be Monitored in 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, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the subject at unnecessary risk from continued administration of study drug/vaccine.
- The subject has a confirmed positive serum pregnancy test.
- The subject is identified as having used illicit drug(s) at any time during the trial.
- The subject is not responding to study medication and requires rescue therapy, in the assessment of the investigator.
- The subject has cellulitis/erysipelas or major cutaneous abscess and is found to have a gram-negative pathogen that requires antibiotic therapy.

- The subject has a wound infection and is found to have gram-negative pathogen that requires antibiotic therapy *and no gram-positive pathogen*; or has coinfection with both gram-positive and gram-negative organisms requiring gram-negative coverage and cannot use aztreonam or metronidazole.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.2 – Discontinued Subjects Continuing to be Monitored in the Trial for those procedures to be completed at each specified visit.

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or subject's legally acceptable representative withdraws consent from the trial.
- The subject is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the trial are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject (or their legally acceptable representative) provides documented informed consent. The overall trial ends when the last subject completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the subject is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

5.11 Clinical Criteria for Early Trial Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

Trial Period:	Screening[a]	Treatment						Posttreatment	
Visit Number/Title:	1 Screening[a]	2 Allocation/ Randomization[a]	3 Early Assessment[c]	Phone Contact[b]	4 Day 6	5 Day 10[c]	6 EOT	7 TOC[c]	8 Late Follow-up[c]
Scheduled Day (hours where specified):	-1	1	48-72 Hour		6	10	15	25	35
Scheduling Window (days, except as noted):[d]	-1 or 1	1	48-72 Hour		5 or 6	10 ±1	15-17	22-29	33-40
Administrative Procedures									
Collect Informed Consent/ Assent	X								
Provide subject/caregivers with Subject ID Card (after consent)	X								
Verify Inclusion/Exclusion Criteria	X								
Record Medical and Surgical History	X								
Record ABSSSI-related procedures [e]	X		X		X	X	X	X	X
Record prior and concomitant medications	X		X		X	X	X	X	X
Randomize via IRT		X							
Dispense study drug [f]		X	X		X	X			
Study drug administration [g,h]		X	X		X	X			
Record information from returned diary and study drug packaging[i]			X[i]		X[i]	X[i]	X[i]		
Clinical Procedures/Assessments									
Complete physical examination with neurologic (see Appendix 12.5) and visual acuity (Snellen or equivalent; verbal subjects only) assessments [j]	X						X		
Directed physical examination with neurologic assessment [j]			X[k]		X	X[k]		X[k]	X[k]
Collect resting vital signs (including height and weight at Screening), temperature [l]	X[m]	X	X[k]		X	X[k]	X	X[k]	X[k]

Trial Period:	Screening[a]	Treatment						Posttreatment	
Visit Number/Title:	1 Screening[a]	2 Allocation/ Randomization[a]	3 Early Assessment[c]	Phone Contact[b]	4 Day 6	5 Day 10[c]	6 EOT	7 TOC[c]	8 Late Follow-up[c]
Scheduled Day (hours where specified):	-1	1	48-72 Hour		6	10	15	25	35
Scheduling Window (days, except as noted):[d]	-1 or 1	1	48-72 Hour		5 or 6	10 ±1	15-17	22-29	33-40
Assess for IV-to-oral switch (see Section 7.1.2.3) [n]			X		X	X			
Pain assessment (Wong-Baker FACES for verbal subjects; FLACC for nonverbal subjects; see Appendix 12.7)	X		X[k]		X	X[k]	X		
Assess for treatment extension by blinded investigator (see Section 7.1.2.4)					X (tedizolid phosphate)	X (Comparator)			
Local electrocardiogram[o]	X								
Assess acceptability and palatability of oral suspension (tedizolid phosphate arm only; see Appendix 12.8) [p]		Once only during oral treatment but preferred after the first oral dose.							
Measure lesion size (see Appendix 12.3)	X		X[k]		X	X[k]	X	X[k]	
Assess signs and symptoms of ABSSSI (see Appendix 12.4)	X		X[k]		X	X[k]	X	X[k]	
Perform blinded investigator's assessment of clinical response							X	X	
Assess for clinical relapse by blinded investigator [q]									X
Assess AEs (causality must be assessed by blinded Investigator) [r]	X	X	X		X	X	X	X	X
Laboratory Procedures/Assessments									
Collect ABSSSI site specimen for culture	X[s]	X[s]	X[k,t]		X[k,t]	X[k,t]	X[t]	X[k,t,u]	X[k,t,u]
Collect blood specimen for culture (Cohorts 1-3 only; in Cohort 4 per local standard of care only if clinically indicated)	X				X[v]		X[v]		
Collect blood sample for PK analysis (Cohorts 1-3) [w]		X			X				

Trial Period:	Screening[a]	Treatment						Posttreatment	
Visit Number/Title:	1 Screening[a]	2 Allocation/ Randomization[a]	3 Early Assessment[c]	Phone Contact[b]	4 Day 6	5 Day 10[c]	6 EOT	7 TOC[c]	8 Late Follow-up[c]
Scheduled Day (hours where specified):	-1	1	48-72 Hour		6	10	15	25	35
Scheduling Window (days, except as noted):[d]	-1 or 1	1	48-72 Hour		5 or 6	10 ±1	15-17	22-29	33-40
Collect blood sample for PK analysis (Cohort 4) [x]		X			X				
Collect sample for hematology (Cohorts 1-3)	X[y]				X		X		
Collect sample for hematology (Cohort 4)	X[y]						X		
Collect sample for urinalysis	X[y]								
Collect sample for serum chemistry (Cohorts 1-3)	X[y]				X		X		
Collect sample for serum chemistry (Cohort 4)	X[y]						X		
Collect urine (or blood) sample for pregnancy (postmenarchal females only) [z]	X						X		

ABSSSI=acute bacterial skin and skin structure infections; AE=adverse event; BP=blood pressure; ECG=electrocardiogram; eCRF=electronic case report form; EOT=end of therapy; FLACC=Face, Legs, Activity, Cry, Consolability; hCG=human chorionic gonadotropin; HR=heart rate; ID=identification; IRT=interactive response technology; IV=intravenous; LFU=late follow-up; PE=physical examination; PK=pharmacokinetic(s); SAE=serious adverse event; SC=study coordinator; TOC=test-of-cure.

a. Visit 1 (Screening) and Visit 2 (Allocation/Randomization) may occur on the same day.
b. A phone call must be made a day prior to Visit 4 to subjects who were assigned to receive oral tedizolid **NOT TO TAKE THEIR DAILY ORAL TEDIZOLID** prior to the visit to ensure a prior dose PK sample can be collected.
c. Visit 3 may be conducted via a telephone interview for subjects who are no longer hospitalized, unless clinically indicated. Visit 5 may be conducted via a telephone interview, unless clinically indicated. Visit 7 may be conducted via a telephone interview for subjects who have clinical success at Visit 6 with no evidence of worsening. For Visit 8 a telephone interview is acceptable for subjects who do not have symptoms of clinical relapse, new or ongoing AEs/SAEs, or laboratory abnormalities that require an on-site follow-up visit with a healthcare provider. If telephone interview, record questions and responses, and where feasible, investigators are encouraged to utilize video or images to observe the lesion.
d. Scheduling Window indicates the Study Days when the assessments may be performed.
e. ABSSSI-related procedures would include puncture, debridement, and incision/drainage. When clinically indicated, use imaging techniques to rule out osteomyelitis in deep wound infections in proximity to bone or joints.
f. Subjects who are randomized to receive IV tedizolid phosphate will have IV tedizolid phosphate dispensed by IRT every 2 days while they remain on IV treatment; those randomized to receive oral treatment, or who switch from IV-to-oral tedizolid phosphate, will have oral tedizolid phosphate dispensed only once (either at randomization or at the IV-to-oral switch, respectively) regardless of the duration of the oral portion of treatment, and will be provided a study drug diary upon discharge.

Trial Period:	Screening[a]	Treatment						Posttreatment	
Visit Number/Title:	1 Screening[a]	2 Allocation/ Randomization[a]	3 Early Assessment[c]	Phone Contact[b]	4 Day 6	5 Day 10[c]	6 EOT	7 TOC[c]	8 Late Follow-up[c]
Scheduled Day (hours where specified):	-1	1	48-72 Hour		6	10	15	25	35
Scheduling Window (days, except as noted):[d]	-1 or 1	1	48-72 Hour		5 or 6	10 ±1	15-17	22-29	33-40

g. Subjects will receive IV and/or oral tedizolid phosphate for 6 to 10 consecutive days or IV and/or oral comparator for 10 to 14 consecutive days of treatment. Treatment extension up to a maximum of 10 days with tedizolid phosphate or 14 days with comparator is allowed if clinically indicated based on blinded investigator assessment at Visit 4 and Visit 5, as described in Section 7.1.2.4. While subject is receiving IV therapy, flush IV line before and after study drug administration. No other IV therapy should be administered concurrently with the study drug. Monitor the subject for at least 30 minutes postinfusion for AEs.
h. Subjects may be started on either oral or IV study medication, at the investigator's discretion; switch to oral treatment is allowed after the first 24 hours on IV, if subjects meet criteria in Section 7.1.2.3.
i. If oral study drug is dispensed to outpatients or at the time of discharge, then subjects/caregivers must complete a study drug diary. Study drug diary must be used to document the date and time of study drug self-administration. Instruct subject/caregivers on study drug administration, use of diary, and dispense outpatient study drug + diary if appropriate. Subjects are to bring remaining drug packaging and the diary back to the site at Visits 3-6, as applicable. Both SC and subjects/caregivers must date and initialize the study drug diary.
j. Height and weight not required for repeated PEs.
k. Performed if on-site visit only.
l. Perform vital signs assessment prior to the start of study drug infusion. Vital signs include temperature, HR, respiratory rate, and BP.
m. If multiple temperature readings are obtained and recorded in the source documentation during the Screening period, please record the highest measured in the eCRF.
n. Assessment of switch from IV-to-oral administration in inpatient subjects can be done before the 48-72 hours visit or in between visits.
o. ECGs are not required for neonates but will be collected if available.
p. Assess acceptability and palatability of the oral formulation of tedizolid phosphate one time only, on one of these visits (applies only to those subjects taking oral tedizolid phosphate). See Appendix 12.8 for scale.
q. Assessment of clinical relapse will be done if there is clinical success at EOT and TOC.
r. The AE reporting period is from the time documented informed consent is provided through LFU (Study Day 35; Visit 8). AE/SAE causality must be assessed by a blinded investigator who is a qualified physician. SAEs should be followed through to outcome (stabilization, resolution/death, or consent is withdrawn).
s. At baseline, appropriate ABSSSI specimens will be evaluated with Gram stain and culture and susceptibility testing. Culture for anaerobes should be conducted at sites where this is standard of care. Obtain a specimen at Visit 2 if the Screening (Visit 1) sample was inadequate or not available for testing.
t. Perform after Day 1 only if clinically indicated. After baseline, ABSSSI specimens are only required if there is no improvement in or if there is deterioration of the primary lesion, and if easily accessible.
u. Follow-up ABSSSI cultures are only required at TOC and LFU visits (Visits 7 and 8) where clinically indicated and not deemed a clinical failure at a prior visit.

Trial Period:	Screening[a]	Treatment						Posttreatment	
Visit Number/Title:	1 Screening[a]	2 Allocation/ Randomization[a]	3 Early Assessment[c]	Phone Contact[b]	4 Day 6	5 Day 10[c]	6 EOT	7 TOC[c]	8 Late Follow-up[c]
Scheduled Day (hours where specified):	-1	1	48-72 Hour		6	10	15	25	35
Scheduling Window (days, except as noted):[d]	-1 or 1	1	48-72 Hour		5 or 6	10 ±1	15-17	22-29	33-40

v. For Cohorts 1, 2, and 3 only, collect after baseline only if previously positive or clinically indicated. Blood cultures are required for aerobic pathogens; culture for anaerobic pathogens is required where it is the local standard of care.
w. For Cohorts 1, 2, and 3, PK samples are to be collected as described in Section 7.1.3.2 (Table 8 and Table 9).
x. For Cohort 4, PK samples are to be collected as described in Section 7.1.3.2 (Table 8 and Table 9).
y. Samples may be collected within 7 days prior to start of dosing.
z. If EOT urine test is positive, confirm with a serum hCG test.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent and/or assent (if applicable) be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent/assent (if applicable) from each potential subject or each subject's legally acceptable representative prior to participating in this clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented consent/assent is in place.

7.1.1.1.1 General Informed Consent/Assent

Informed consent/assent given by the subject or their legally acceptable representative must be documented on a consent/assent form. The form must include the trial protocol number, trial protocol title, dated signature, and agreement of the subject (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent/assent form should be given to the subject (or their legally acceptable representative) before participation in the trial.

The initial informed consent/assent form, any subsequent revised informed consent/assent form, and any written information provided to the subject must receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the subject's or the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population are to be included in the trial informed consent/assent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The assent, as applicable, will adhere to IRB/ERC requirements, applicable laws and regulations, and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies/continues to qualify for the trial at randomization.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject (or their legally acceptable representative) provides documented informed consent/assent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical and surgical history will be obtained by the investigator or qualified designee. This should include collection of any history of skin infection within the 6 months prior to study (as applicable based on age).

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, and record prior medication taken by the subject within 30 days before first infusion of study drug. Subjects with more than 24 hours of prior antibacterial therapy are excluded per exclusion criterion 3 (Section 5.1.3 and Section 5.5).

Note: Breastfed subjects should be excluded if the mother is receiving these excluded medications

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

Concomitant therapies are to be recorded as follows:

- All concomitant medications used within 30 days before the first infusion of study drug through the 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 ABSSSI within

2 days before the first administration 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 AE

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Specific details on the Screening Visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance (Medication)

Study drug compliance will be monitored. For inpatients, investigator and/or trial staff will be responsible for administration of trial medication and will record administration in the subject's CRF. For outpatients, the study drug administration will be entered in the subject's diary card, which will be checked by the site staff at each study visit.

Interruptions from the protocol-specified treatment plan for ≥2 days of study therapy consecutively require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Exam

Physical Exams will be conducted as per the Trial Flow Chart – Section 6.0. All physical exams will include height and weight (at Screening), and vital signs (BP, HR, respiratory rate, and temperature [oral, tympanic, or rectal, etc.]).

Neurologic examination will be assessed using the criteria in Appendix 12.5.

Visual acuity will be evaluated in verbal subjects only, using Snellen or an equivalent exam.

Note: Consistent method should be used to obtain body temperature, and the subject should be in the same resting position for all vital sign measurements.

7.1.2.2 Assessment of Pain

Pain will be assessed at time points indicated in the Trial Flow Chart - Section 6.0 using the Wong-Baker FACES pain rating scale for verbal subjects or the FLACC behavioral pain rating scale for nonverbal subjects. Both are provided in Appendix 12.7.

7.1.2.3 Assessment for IV-to-Oral Switch

Subjects initiated on IV study medication will be evaluated for potential switch to oral therapy. Switch to oral therapy will be allowed 24 hours after the first IV dose. 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 length, or width
- Last temperature is <37.7°C
- Signs or symptoms of the primary ABSSSI site (Appendix 12.4) have not worsened and at least 1 has improved from baseline

7.1.2.4 Assessment for Treatment Extension

All subjects will be evaluated by the blinded investigator at Visit 4 (final day [Day 5 or 6] of dosing in the tedizolid phosphate arm) and Visit 5 (final day [Day 10 ±1 day] of dosing in the comparator arm) for a potential extension of treatment of up to 4 days. To maintain the blind, this assessment must be performed for all subjects at both visits, unless no need for extension is determined at Visit 4, in which case, the subject does not need to be reassessed for extension at Visit 5. Unblinded staff (Section 5.2.3) will manage all dosing in both treatment arms and, if applicable, implement the extension based on the treatment arm.

Based on prior efficacy results in adults and adolescents, it is the expectation that 6 days' therapy with tedizolid phosphate or 10 days' therapy with comparator will be sufficient to provide a satisfactory clinical response. Subjects for whom the blinded investigator determines an extension to be clinically indicated will have treatment extended up to 4 days. Subjects for whom the investigator determines that extension of treatment is not clinically indicated should **not** have treatment extended.

The investigator may consider the following criteria for pronounced improvement from baseline in evaluating the clinical need for a treatment extension:

- Marked reduction from baseline (~40% or more) in primary lesion size
- For verbal subjects, ≥2-point decrease from baseline or score of 0 on the Wong-Baker FACES pain rating scale for the primary lesion (see Appendix 12.7 for pain scales). Note: There is not a similar criterion for nonverbal subjects since the FLACC score is behavioral and nonspecific with respect to the source of distress.
- Has no new signs or symptoms of ABSSSI and no complications attributable to ABSSSI compared with baseline.

7.1.2.5 Lesion Evaluation, Symptoms Recording, and Treatment Response Assessment

The primary lesion will be measured, assessed, and recorded for signs and symptoms of ABSSSI and clinical response, as described in Section 7.1.2.5.1 to Section 7.1.2.5.4.

Any secondary lesion observed at the Screening Visit should be reported as medical history. Any secondary lesion first observed or worsening after randomization should be reported as an AE.

7.1.2.5.1 Measurement of Lesion Size

Lesion size will be assessed using the method provided in Appendix 12.3 and recorded in the subject CRF at the time points indicated in the Trial Flow Chart - Section 6.0. The same site personnel should preferably measure lesion size for a subject throughout the study.

7.1.2.5.2 Recording of Signs and Symptoms of ABSSSI

Signs and symptoms of ABSSSI will be assessed per the instructions provided in Appendix 12.4 and recorded in the subject CRF at the time points indicated in the Trial Flow Chart - Section 6.0.

7.1.2.5.3 Clinical Response Assessment

Efficacy will be assessed via the blinded investigator's assessment of clinical success at the EOT and TOC Visits. A subject assessed as a clinical failure at any time during the study is considered a clinical failure at the TOC Visit and will not be reassessed. Response definitions for the investigator's assessment and the programmatic assessment are provided in Table 4 and Table 5.

Table 4 Investigator's Assessment of Clinical Response Definitions (EOT and TOC Visits)

Term	Definition
Clinical Success	**All of the following:** • Resolution or near resolution of most disease-specific signs and symptoms • Absence or near resolution of regional or systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal white blood cell count), if present at baseline • No new signs, symptoms, or complications attributable to the infection under study, therefore, no further antibiotic therapy is required for the treatment of the primary lesion
Clinical Failure	**Any of the following:** • Requires additional antibiotic therapy for treatment of the primary lesion • Unplanned major surgical intervention required due to failure of study drug (ie, amputation) • Developed osteomyelitis after baseline • Persistent gram-positive pathogen bacteremia • TEAE leading to discontinuation of study drug and subject required additional antibiotic therapy to treat the infection under study • Death (all-cause mortality) within 28 days of first infusion

Term	Definition
Indeterminate	**Study data are not available for the evaluation of efficacy for any reason including:** • Osteomyelitis present at baseline • Subject lost to follow-up • Extenuating circumstances that preclude the classification of a clinical success or failure • For subjects with cellulitis/erysipelas or major cutaneous abscess: Gram-negative organism isolated at baseline that required a different antibiotic therapy • For subjects with wound infections: Gram-negative organism isolated at baseline that required a different antibiotic therapy other than aztreonam or metronidazole • Subject withdraws consent

EOT=end of therapy; TOC=test-of-cure

Table 5 Programmatic Assessment of Clinical Response Definitions (48-72 Hour Visit)

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

7.1.2.5.4 Clinical Relapse Assessment

Relapse will be evaluated at the LFU Visit only in subjects who have clinical success at EOT and TOC Visits using the definitions provided in Table 6.

Table 6 Investigator's Assessment of Clinical Relapse Definitions (Late Follow-up Visit)

Term	Definition
Sustained Clinical Success	No new signs or symptoms of primary ABSSSI after TOC
Relapse	New or worsened signs or symptoms of primary ABSSSI after TOC
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including the following: • Subject lost to follow-up • Extenuating circumstances that preclude the classification of a clinical success or relapse • Subject withdraws consent

ABSSSI=acute bacterial skin and skin structure infections; TOC=test-of-cure

7.1.2.6 Electrocardiogram

A local ECG (minimal 5-lead ECG) will be required for all subjects except neonates at Screening*. A prestudy ECG may be used if it was performed and documented within 1 month prior to enrollment.

*Note: Available ECG data will be reviewed.

7.1.2.7 Assessment of Acceptability and Palatability of Oral Suspension

Acceptability and palatability of the tedizolid phosphate oral suspension will be assessed once, per the Trial Flow Chart - Section 6.0, using the criteria in Appendix 12.8, and recorded on the CRF.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be collected over the course of the trial (from pretrial to posttrial visits), including approximate blood volumes collected by visit and by sample type per subject can be found in Appendix 12.2 (Table 17).

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 7. Samples collected within 7 days prior to start of dosing will be acceptable. In addition, urine pregnancy tests will be performed for postmenarchal females.

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis
Hematocrit	Albumin	Urine human chorionic gonadotropin (hCG) (serum test also acceptable)
Hemoglobin	Alkaline phosphatase	Blood
Platelet count	Alanine aminotransferase (ALT)	Glucose
WBC (total and differential)	Aspartate aminotransferase (AST)	Protein
	Bicarbonate	Specific gravity
	Calcium	Microscopic exam, if abnormal results are noted
	Chloride	
	Creatinine	
	Glucose	
	Phosphorus	
	Potassium	
	Sodium	
	Total Bilirubin	
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal	
	Total protein	
	Blood Urea Nitrogen	

Clinical laboratory safety tests and pregnancy tests, when applicable, will be performed at the local laboratory at time points specified in the Trial Flow Chart - Section 6.0.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

Sparse PK sampling will be obtained in all tedizolid-treated subjects to characterize the population PK of tedizolid in subjects from birth to <12 years of age. The timing for PK sampling by visit for subjects receiving once-daily dosing and for subjects receiving twice-daily daily dosing is set out in Table 8 and Table 9, respectively (refer to Section 6.0 for the schedule and Appendix 12.2 for volumes).

Typical PK parameters, inter-individual and residual variability, and the effects of individual-specific covariate factors of tedizolid PK will also be estimated. These analyses will be reported separately. Detailed instructions on collecting and processing blood PK samples are provided in the PK section of the laboratory manual.

In subjects receiving one daily dose based on body weight (see Table 2), a total of 4 samples are to be collected from each subject, as follows:

- 2 samples at Visit 2 (after the first dose)
- 2 samples at Visit 4 to provide a trough (predose) and a mid-peak sample

Table 8 PK Sampling Instructions for Subjects Receiving Once-daily Dosing

Visit No.	Sample No.	First dose IV	First dose oral[a]
Visit 2	Sample 1	Collect 1 sample between 5 and 80 minutes after the end of infusion	Collect 1 sample between 4 and 12 hours after dosing
	Sample 2	Collect a second sample between 4 and 12 hours after infusion	Collect a second sample between 4 and 12 hours after dosing, at least 90 minutes after the first sample
Visit 4[b]	Sample 1	Collect 1 sample immediately prior to dosing (trough)	
	Sample 2	Collect a second sample between 4 and 12 hours after dosing	

AE=adverse event; IV=intravenous; PK=pharmacokinetic(s)

Note: PK samples should only be collected from subjects receiving tedizolid phosphate regardless of route of administration.

a If the subject vomits during and/or within 1.5 hours of oral dose administration, PK samples will not be collected. However, vomiting must be recorded as an AE.

b A phone call must be made a day prior to Visit 4 to remind subjects who are on oral tedizolid **not to take** their daily oral tedizolid prior to the site visit to ensure that a predose PK sample can be collected. Please refer to Section 6.0 - Trial Flow Chart.

In Cohorts 1, 2, and 3, in subjects receiving twice-daily doses (q12h) based on body weight (see Table 2), a total of 4 samples are to be collected from each subject, as follows:

- 2 samples at Visit 2 (after the first dose)
- 2 samples at Visit 4; one sample should be within 1 hour prior to either daily dose to provide a trough (predose) and a mid-peak sample after either daily dose

In Cohort 4, a total of 3 samples are to be collected from each subject, as follows:

- 1 sample at Visit 2 (after the first dose)
- 2 samples at Visit 4; one sample should be within 1 hour prior to either daily dose to provide a trough (predose) and a mid-peak sample after either daily dose

Table 9 PK Sampling Instructions for Subjects Receiving Twice-daily (q12h) Dosing

Visit No.	Sample No.	First dose IV	First dose oral [a]
Cohorts 1, 2, and 3			
Visit 2	Sample 1	Collect 1 sample between 5 and 80 minutes after the end of infusion	Collect 1 sample between 4 and 8 hours after dosing
	Sample 2	Collect a second sample between 4 and 8 hours after infusion	Collect a second sample between 4 and 12 hours after dosing, at least 90 minutes after the first sample and prior to second dose
Visit 4	Sample 1	Collect 1 sample within 1 hour prior to either daily dose (at least 11 hours after previous dose).	
	Sample 2	Collect a second sample between 4 and 8 hours after either daily dose	
Cohort 4			
Visit 2	Sample	Collect 1 sample between 5 and 80 minutes after the end of infusion	Collect 1 sample between 4 and 8 hours after dosing
Visit 4	Sample 1	Collect 1 sample within 1 hour prior to either daily dose (at least 11 hours after previous dose).	
	Sample 2	Collect a second sample between 4 and 8 hours after either dose	

AE=adverse event; IV=intravenous; PK=pharmacokinetic(s)

Note: PK samples should only be collected from subjects receiving tedizolid phosphate regardless of route of administration.

a If the subject vomits during and/or within 1.5 hours of oral dose administration, PK samples will not be collected. However, vomiting must be recorded as an AE.

The post-Visit 2 samples will capture PK in the multiple-dose setting. Four samples per subject will provide minimally 80 samples in Cohort 3 (28 days to <2 years), which is slated to enroll minimally 20 subjects on oral and/or IV tedizolid phosphate, providing sufficient samples to evaluate concordance of these data with data from the prior Phase 1 study in this population. Three samples per subject in Cohort 4 (from birth to <28 days of age) will provide sufficient samples to evaluate PK while minimizing the number and total volume of blood draws in this preterm and term neonate population.

7.1.3.3 Sample Collection for Microbiology Assessments

Sampling for microbiology assessments will be at the time points in the Trial Flow Chart - Section 6.0. Microbiological specimens are to be sent to the local laboratory for culture and isolation. For randomized subjects all bacterial isolates locally deemed contributory (pathogenic) to the infectious process for the disease under study will be shipped to the Central Microbiology Laboratory for confirmatory identification and susceptibility testing (Table 10).

Specimens for culture are required for abscesses and wounds at Screening; cellulitis specimens are to be collected if this is standard practice at the site.

For required blood cultures, at least one aerobic blood culture is required; anaerobic blood culture should only be taken where this is the local standard of care.

Table 10 Samples for Microbiology Assessments

Sample	Laboratory		Comments[a]
	Local	Central[b]	
Appropriate ABSSSI site specimen			All samples collected for microbiological assessment must be collected via valid sampling technique (aspirate, biopsy, deep swab, etc.); superficial swab not acceptable.
Gram stain, isolation/culture, and storage/archiving of pure pathogens (-20°C/-80°C)	**X**		
Isolates from local laboratory culture for confirmation of identification and susceptibility testing		**X**	Send all isolates from the local laboratory culture to the central laboratory except for those listed as never a pathogen in Appendix 12.6.
Blood Cultures			Collect 1 vial for aerobic testing and 1 for anaerobic testing (anaerobic testing only if within local standard of care).
Gram stain (optional), isolation/culture, and storage/archiving of pure pathogens (-20°C/-80°C)	**X**		Send both vials to local laboratory.
Isolates from blood culture for confirmation of identification and susceptibility testing		**X**	Send all isolates from a local laboratory culture to the central laboratory. If blood culture is positive, repeat within 24 hours.

ABSSSI=acute bacterial skin and skin structure infections

a Further instructions are provided in Appendix 12.6.

b The study site is to send isolates deemed contributory (pathogenic) to the infectious process to the central laboratory only for subjects who will be randomized; do not send isolates from subjects who fail Screening.

Data from these cultures will be used to assess the microbiological response, per Table 11. Note that the microbiological response will be determined programmatically by the Sponsor, and not by the investigator or site.

Table 11 Microbiological Response Definitions

Term	Definition
Eradication	Absence of original baseline pathogen(s)
Presumed Eradication	No source specimen to culture in a subject assessed as a clinical success by the investigator
Persistence	Continued presence of the original baseline pathogen(s)
Presumed Persistence	No source specimen to culture in a subject assessed as a clinical failure by the investigator
Recurrence	Identification of original baseline pathogen(s) after clearance
Indeterminate	The subject's clinical response is indeterminate or other circumstance that precludes a microbiological evaluation
Superinfection	Isolation of a nonbaseline pathogen from the primary ABSSSI site (excluding superficial swabs) while the subject is receiving study drug and the subject has worsening or new signs or symptoms of the primary ABSSSI
New infection	Isolation of a nonbaseline pathogen from a posttreatment culture from the primary ABSSSI site (excluding superficial swabs) in a subject with worsening or new signs or symptoms of the primary ABSSSI

ABSSSI=acute bacterial skin and skin structure infections

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a subject withdraws from participation in the study, all applicable activities scheduled for the next planned efficacy visit (EOT, TOC, or LFU) should be performed (at the time of withdrawal). Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2. If a subject withdraws assent (or parents/LAR withdraw consent) for participating in the trial, only AE information (and no further study assessments) should be collected, to the extent consent remains for this.

7.1.4.2 Blinding/Unblinding

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY

EFFORT SHOULD BE MADE NOT TO UNBLIND THE PARTICIPANT UNLESS NECESSARY.

For emergency situations where the investigator or delegate needs to identify the drug used by a participant and/or the dosage administered he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator or delegate should make reasonable attempts to enter the intensity grade of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed. In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

7.1.4.3 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Approximately 1 day prior to treatment allocation/randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1.

Note that Screening and allocation/randomization may be performed on the same day. Prescreening local laboratory test results that were collected as part of standard of care may be used if collected within acceptable windows as specified in the laboratory manual.

Rescreen is permitted once if a subject initially does not meet eligibility but later does. However, the original screening number must be retained, and age eligibility will be based upon rescreen date.

7.1.5.2 Discontinued Subjects Continuing to be Monitored in the Trial

As noted in Section 5.8.1, discontinuation from treatment does not equate to discontinuation from study. In most cases, all study procedures and assessments should be conducted even if the subject is discontinued early from treatment (other than study drug administration, IV-to-oral switch assessment, study drug extension assessment, PK sample collection, and study drug acceptability/palatability), as per the Trial Flow Chart - Section 6.0.

Exceptions are as follows:

- Removal of consent/assent: no further assessments are conducted (although if the subject permits, any existing AEs should be followed as outlined in Section 7.2).
- Presence of gram-negative pathogen requiring treatment which, for scenarios outlined in Section 5.8.1, requires discontinuation of study medication and initiation of rescue medication with gram-negative activity: only safety assessments (clinical labs, physical exams/vital sign measurements, neurological exams, visual acuity exams, AEs, concomitant medications) need to be conducted. Efficacy assessments (such as lesion size measurements and clinical response and relapse assessments) should be skipped as these subjects are, by definition, indeterminate (Table 4).

7.1.5.3 Post-Therapy

While Visit 6 (EOT) must be in-person, telephone interviews are allowed for Visit 7 (TOC) and Visit 8. Visit 7 may be conducted via a telephone interview for subjects who have clinical success at Visit 6 with no evidence of worsening and Visit 8 may be conducted as a telephone interview 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.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor’s product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the subject (or their legally authorized representative) provides documented consent but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through the last visit of the trial (Late Follow Up), all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose of tedizolid phosphate is any dose higher than 1.25 times the nominal dose (nominal doses are defined in Section 5.2). This threshold was selected conservatively as a dosage expected to produce an exposure (AUC) that matches the exposure reached at the no-observable-adverse-effect level in juvenile rats after 6 weeks of dosing (rats dosed from postnatal Day 7 through 56). An overdose of centrally sourced or locally sourced comparators (Section 5.2) is any dose higher than 2 times the nominal prescribed dose per local guideline.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other serious criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious adverse event, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the subject (or their legally authorized representative) provides documented consent but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through the last visit of the trial (Late Follow Up) must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 13 for additional details regarding each of the above criteria.

For the time period beginning after the subject (or their legally authorized representative) provides documented consent until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure..

For the time period beginning at treatment allocation/randomization through the last visit of the trial (Late Follow Up), any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be

reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning after the subject (or their legally authorized representative) provides documented consent until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through the last visit of the trial (Late Follow Up), any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

2. Severe or serious cases of *Clostridium difficile* infection such as toxic megacolon or pseudomembranous colitis

3. Clinically significant hematologic AEs, defined as cutoff values for hemoglobin, platelet count, or absolute neutrophil count by age (Table 12). For all subjects except preterm neonates, these cutoffs are based on grade 2 low values as categorized in the US National Institutes of Health, Division of AIDS, AE grading scale for adults and children

(version 2, 2014). For preterm neonates, clinically significant low values for these parameters are per local standards.

Table 12 Cutoff Values for Hematological Events of Clinical Interest by Age

Laboratory Test by Age	Cutoff Value
Hemoglobin	
57 days to <13 years	<9.5 g/dL
36 to 56 days	<8.5 g/dL
22 to 35 days	<9.5 g/dL
8 to 21 days	<11 g/dL
<8 days	<13 g/dL
Platelet Count	
Any age	$<1 \times 10^5$ cells/mm^3
Absolute Neutrophil Count	
>7 days	<800 cells/mm^3
2 to 7 days	$<1.250 \times 10^3$ cells/mm^3
≤1 day	$<4.000 \times 10^3$ cells/mm^3

4. Serotonin syndrome in subjects receiving drugs with serotonergic potential
5. Peripheral neuropathy
6. Optic neuropathy
7. Lactic acidosis (elevated serum L-lactate level) or unexplained metabolic acidosis
8. Emergence of drug resistance
9. Unusual lack of efficacy, including bacteremia or progression of infection after 3 days of therapy, or treatment failure in immunocompromised subjects (eg, subjects with ANC <1000 cells/mm^3 or subjects receiving immunosuppressive therapy)

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 13. The investigator's assessment of causality is required for each adverse event. Refer to Table 13 for instructions in evaluating adverse events.

Table 13 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 Trial Governance and Oversight

7.3.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the external Data Monitoring Committee (DMC) regarding the trial.

7.3.2 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor's study team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor's study team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes are made to primary and secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the sSAP) will be developed to detail other planned analyses (ie, those specific to the analysis of PK data).

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 8.2 to Section 8.12.

Study Design Overview	A Phase 3 randomized, assessor-blind, active-comparator-controlled clinical trial to study the safety and efficacy of MK-1986 (tedizolid phosphate) and comparator, in subjects from birth to <12 years of age with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)
Treatment Assignment	Subjects from birth to <12 years of age with ABSSSI will be stratified and enrolled into 4 cohorts based on age (Cohort 1, 6 years to <12 years; Cohort 2, 2 years to <6 years; Cohort 3, 28 days to <2 years, Cohort 4, from birth to <28 days [term and preterm neonates*]). * Gestational age should be at least 26 weeks at birth. Subjects will be randomized, in a 3:1 ratio, to tedizolid phosphate (IV and/or oral) 200 mg per day for 6 to 10 days or to comparator (IV and/or oral) for 10 to 14 days. Treatment can be extended up to a maximum of 10 days of tedizolid phosphate or 14 days of comparator if clinically indicated based on blinded investigator assessment at Visit 4 (final day [Day 5 or 6] of dosing in the tedizolid phosphate arm) and Visit 5 (final day [Day 10 ±1 day] of dosing in the comparator arm). Subjects may be initiated on either IV or oral therapy, at the discretion of the investigator, although at least 50% of subjects in each arm must receive at least 24 hours of IV therapy. Stratification will include at least 36 subjects in Cohort 1 treated with tedizolid phosphate (corresponding to at least 48 subjects overall), at least 24 subjects in Cohort 2 treated with tedizolid phosphate (corresponding to at least 32 overall), and at least 20 subjects in Cohort 3 treated with tedizolid phosphate (corresponding to at least 27 overall). There is no minimum number of subjects required for Cohort 4.
Analysis Populations	Efficacy: Intent to Treat (ITT), Clinically Evaluable at Test-of-Cure (CE-TOC), Microbiological ITT (MITT), and Microbiologically Evaluable (ME) populations Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	The primary endpoint is the overall safety assessment of tedizolid phosphate within the pediatric population. Multiple assessments are conducted to evaluate the safety: ▪ Adverse events (AEs); ▪ Vital signs; ▪ Physical exams including specific neurological and visual acuity assessments; ▪ Hematology and clinical chemistry.
Secondary Endpoint	The investigator's assessment of clinical response at the TOC visit, 22-29 days after the first infusion, in the ITT and CE-TOC populations;

Statistical Methods for Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	No hypothesis testing is planned. The number and percentage of subjects who have an investigator's assessment of clinical success, clinical failure, and indeterminate response at TOC in the ITT and CE-TOC populations (by definition, subjects in the CE-TOC population cannot have an indeterminate response) will be summarized for each treatment group. An exact two-sided 95% confidence interval (CI) will be provided for the rate of early clinical response in each treatment group using the Clopper-Pearson method. The difference between treatment groups in the rate of clinical success will be estimated, as will a two-sided 95% CI for the treatment difference using the method of Miettinen and Nurminen stratified by age cohort.
Statistical Methods for Safety Analyses	Prespecified Tier-1 AEs include the standardized MedDRA query (SMQ) "Hematopoietic cytopenias". Tier-2 AEs include any TEAE, any SAE, any Drug-Related AE, any Serious and Drug-Related AE, any Discontinuations due to AE. The incidence of TEAEs 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. Tier-2 AEs will be evaluated using the (unstratified) Miettinen and Nurminen method with 95% confidence intervals for between-treatment differences in the percentage of subjects, if the incidence of these AEs is ≥ 4 subjects in at least one of the treatment groups. Descriptive statistics of clinical laboratory results (hematology and chemistry), vital sign measurements, physical exams (including specific neurological and visual acuity assessments) and the change from baseline will be presented, as will a summary of laboratory information.
Interim Analyses	At a minimum, there will be the planned DMC reviews after the first 5 tedizolid-treated subjects in each cohort have been enrolled, and additionally at 33% and 66% of the total enrollment. DMC will be reviewing accruing data including safety and efficacy during the course of the study. The purpose of these analyses is for the DMC to review safety data, with no formal stopping criteria for efficacy or safety. An interim analysis to assess safety, efficacy, and PK may be performed when subjects from Cohorts 1 and 2 complete the study.
Multiplicity	No multiplicity adjustment for testing multiple endpoints or multiple interim analyses is planned as the primary endpoint is to assess the safety.
Sample Size and Power	The planned sample size is approximately 100 subjects to ensure that at least 75 subjects receive tedizolid phosphate and are evaluable for safety; subjects not evaluable for safety will replaced. With an estimated drop-off rate of 5%, 95 subjects are expected to receive study treatment. With 72 subjects receiving tedizolid phosphate, the probability of detecting at least one SAE with a true underlying incidence rate of 2% is 77% [6].

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor or its designee.

This trial is being conducted as a randomized, assessor-blind study, ie, a blinded assessor(s) at the site will not know the treatment assignment administered; however, the unblinded investigator(s), unblinded site staff, subject, and Sponsor personnel will be aware of the group assignments.

The randomized allocation schedule will be generated by an external vendor and implemented by the vendor of the study IRT.

8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0. No hypothesis will be tested as part of this trial.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are summarized in Section 4.2.3.1 to Section 4.2.3.4.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Intent to Treat (ITT) population will serve as the primary population for the analysis of efficacy data in this study. The ITT population consists of all randomized subjects.

The CE-Test-of-Cure (CE-TOC) population will be used in the analysis of the secondary efficacy endpoint. The CE-TOC population will include data from randomized subjects who meet all of the following criteria:

- Have a confirmed ABSSSI clinical diagnosis;
- Have a suspected or documented gram-positive infection from baseline Gram stain or culture;
- Met all other inclusion criteria and met no exclusion criteria;
- Have received a sufficient course of therapy:
    - Received at least 48 hours of dosing with study drug and the correct study drug based on the randomization assignment
- Completed EOT, and TOC investigator's assessments (unless assessed as failures at any time point before the TOC Visit)
- 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.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using both the ITT and CE-TOC populations. Details on the approach to handling missing data are provided in Section 8.6.1.2.

The Microbiological Intent to Treat (MITT) and Microbiologically Evaluable (ME) populations will serve as the exploratory populations for the analysis of efficacy data and the

microbiological outcomes in this study. Subjects will be included in the treatment group to which they are randomized for both populations.

The MITT population consists of all randomized subjects with at least one gram-positive pathogen at baseline.

The ME population includes data from subjects in the MITT population who are also in the CE-TOC population.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 Statistical Methods

Statistical methods for the analysis of efficacy endpoints are provided in protocol Section 8.6.1. Statistical testing and inference for safety analyses are described in Section 8.6.2.

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations (SDs), medians, minimums, and maximums for continuous variables will be provided. All comparisons will be for tedizolid phosphate versus comparator.

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the secondary objective. Descriptive statistics will be provided for the exploratory endpoints.

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-TOC population.

8.6.1.1 Efficacy Endpoints

The secondary efficacy endpoint is the following:

- The investigator's assessment of clinical response at the TOC visit, 22-29 days after the first infusion, in the ITT and CE-TOC populations.

The main efficacy outcome is the investigator's blinded assessment of clinical response at the TOC Visit on Day 25 (range from 22-29 days) after the first treatment in the ITT and CE-TOC populations. A subject assessed as a clinical failure at any time during the study is

considered a clinical failure at the TOC Visit. The number and percentage of subjects who have an 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) populations will be summarized for each treatment group. An exact two-sided 95% CI will be provided for the rate of clinical success in each treatment group using the Clopper-Pearson method. The difference between the treatment groups in the rate of clinical success will be estimated, as will a two-sided 95% CI for the treatment difference using the method of Miettinen and Nurminen stratified by age cohort.

An interim analysis may be performed when subjects from Cohorts 1 and 2 complete the study. The difference between the treatment groups in the rate of clinical success will be estimated, as will a two-sided 95% CI for the treatment difference using the method of Miettinen and Nurminen without stratification.

8.6.1.2 Handling of Missing Data

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

For the main efficacy outcome measure of 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 population, indeterminates are included in the denominator and are thus considered clinical failures.

For the main efficacy outcome measure of 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 below in Table 14.

Table 14 Investigator's Assessment of Clinical Response Determination Considering Missing Data

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

EOT=end of therapy; TOC=test-of-cure

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

For the analysis in the ITT population of 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 population.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), vital signs, physical exams including specific neurological assessments, hematology and clinical chemistry.

Continuous measures such as changes from baseline (or percent change from baseline as appropriate) in vital signs, hematology, and clinical chemistry will be summarized in table format by treatment group/arm. Baseline will be defined based on the last available measurement prior to randomization.

Abnormal physical examination findings will be summarized by body system and visit with frequency tables. Neurologic examination and visual acuity examination data will be summarized by visit with frequency tables.

The tiers differ with respect to the analyses that will be performed (Table 15). Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance, with p-values and 95% confidence intervals provided for between-group comparisons.

Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates, with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Based on the number of events, observed adverse experiences and other safety parameters will be classified as belonging to either "Tier 2" or "Tier 3". Membership in Tier 2 requires that at least 4 subjects in at least one treatment group exhibit the event; all other AEs and other safety parameters will belong to Tier 3. The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will include zero when each treatment group has less than 4 events and thus would add little to the interpretation of potentially meaningful differences.

Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures, such as changes from baseline in vital signs, hematology, and clinical chemistry that are not prespecified as Tier-2 endpoints, will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

95% confidence intervals (Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the unstratified Miettinen and Nurminen method [7], an unconditional, asymptotic method. If events do not meet minimum frequency criteria, as determined by the commonly occurring event definition, only point estimates will be provided.

Table 15 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	SMQ of "Hematopoietic cytopenias"	X	X	X
Tier 2	Any TEAE		X	X
	Any SAE		X	X
	Any drug-related AE		X	X
	Any serious and drug-related AE		X	X
	Discontinuation due to AE		X	X
Tier 3	Change from Baseline Results (Vital Signs, Hematology, Clinical Chemistry)			X
	Incidence of subjects with potentially clinically significant abnormal hematology parameters (ECIs, as defined in Table 12)			X

AE=Adverse event, referring to both clinical and laboratory AEs; CI=confidence interval; ECI=event of clinical interest; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious AE; SMQ= standard MedDRA query, TEAE=treatment-emergent AE; X=results will be provided

An interim analysis may be performed when subjects from Cohorts 1 and 2 complete the study. Events that are described above as either Tier 1, 2, or 3 events will be summarized descriptively.

8.6.3 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (age, race, sex), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment group using descriptive statistics for continuous or categorical variables, as appropriate.

8.7 Interim Analyses

At a minimum, there will be planned DMC reviews after the first 5 tedizolid-treated subjects in each cohort have been enrolled, and additionally at 33% and 66% of the total enrollment. DMC will be reviewing accruing data including safety and efficacy, during the course of the study (see Section 7.3.2). The purpose of these analyses is for the DMC to review safety data, with no formal stopping criteria for efficacy or safety.

An interim analysis to assess safety, efficacy, and PK may be performed when subjects from Cohorts 1 and 2 complete the study.

8.8 Multiplicity

The primary objective of the study is to evaluate the safety of tedizolid phosphate, the study is not powered for inferential statistics, and the summaries provided are descriptive in nature. Therefore, there will be no multiplicity adjustment for testing multiple endpoints or multiple interim analyses.

8.9 Sample Size and Power Calculations

The planned sample size is 100 subjects. With an estimated drop-off rate of 5%, 95 subjects are expected to receive the study treatment. See Section 2.1 and Section 4.2.1 for the minimum number of subjects to receive tedizolid phosphate in each cohort.

The probability of observing at least one SAE in this study depends on the number of subjects receiving tedizolid phosphate and the underlying percentage of subjects with a SAE in the study population. If the underlying incidence of a SAE is 2% (1 of every 50 subjects receiving tedizolid phosphate), there is a 77% chance of observing at least one SAE among 72 subjects in the tedizolid phosphate treatment group [6].

8.10 Subgroup Analyses and Effect of Baseline Factors

To assess the consistency of the treatment effect across various subgroups, the estimate of the between-treatment differences in the percentage of subjects (with a nominal 95% CI using the unstratified Miettinen and Nurminen method) for the for the primary safety and efficacy endpoints will be estimated and plotted within each category of the following classification variables:

- Age category (6 to <12 years, 2 to <6 years, 28 days to <2 years, birth to <28 days [term and preterm neonates; if sufficient number of subjects])
- Sex (female, male)
- Race (white, non-white)
- Region
- Inpatient vs. outpatient status at baseline
- Subjects receiving IV only vs. those that received IV-to-PO or PO only
- By type of infection (cellulitis, abscess, wound infection)
- Treatment duration (≤8 days vs. >8 days)

Subgroup analysis and subgroup plots may exclude categories which accrue <15% of the ITT subjects (ie, <15 out of 100 subjects) as the exploration of such small sample sizes are considered to be non-informative in nature.

8.11 Compliance (Medication Adherence)

In this trial, as part of the routine recording of the amount of trial treatment taken by each subject, the number of trial medication doses will be reviewed and recorded at regular intervals. These results will be used to calculate subject compliance.

A subject will be considered 100% compliant on a given day only if daily doses of trial medication (ie, once-daily dose in subjects with body weight ≥50 kg and twice-daily [q12h] doses in subjects with body weight <50 kg) is recorded. Therefore, the rate of compliance will be a function of the total number of doses while on therapy, to be calculated using the following formula:

> Percent Compliance = 100 x the recorded number of doses of trial medication while on therapy, divided by the expected number of doses while on therapy.

The days on therapy includes the interval of days from the first day of dosing to the last day of dosing of trial medication, whether the subject completes the full scheduled trial regimen or discontinues early. Days of follow-up after discontinuation of trial treatment are not included in the compliance calculation.

Summary statistics will be provided on percent compliance by treatment group for the ASaT population.

8.12 Extent of Exposure

Duration of subject exposure to randomized treatment will be summarized, by treatment group, across intervals of time through the last observed exposure interval. In addition, summary statistics (n, median, minimum and maximum) for duration (in days) will be provided.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in the pharmacy manual.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

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

Intravenous Form

Tedizolid phosphate is formulated as a sterile lyophilized powder for injection for IV administration. Further information is provided in the IB and Table 16.

Oral Form

Tedizolid phosphate is also formulated as a white powder for constitution into a suspension for oral administration. Further information is provided in the IB and Table 16.

Comparator study drugs are provided by the site for both IV and oral administration, with selection and dose as recommended in the protocol (Table 2). For sites that are not permitted

by local regulation or are otherwise unable to supply the comparators, MSD will arrange the supply of the appropriate comparator drugs. The IV comparators are vancomycin, linezolid (outside the EU only), clindamycin, flucloxacillin, and cephazolin (cefazolin). The oral comparators are linezolid (outside the EU only), clindamycin, flucloxacillin, and cephalexin (cefalexin).

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.

These products should be used as directed in their package inserts. IV administration of metronidazole is acceptable.

Table 16 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Tedizolid phosphate (200 mg)	200 mg per vial (IV)	Provided centrally by the Sponsor
Tedizolid phosphate (20 mg/mL)	2000 mg per bottle (Powder for Oral Suspension)	Provided centrally by the Sponsor
Vancomycin	IV	Provided locally by the trial site. 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.
Linezolid *	IV or oral	
Clindamycin	IV or oral	
Flucloxacillin	IV or oral	
Cephazolin (Cefazolin)	IV	
Cephalexin (Cefalexin)	Oral	

EU=European Union; IV=intravenous
* For use outside the EU only, as not approved for pediatric use in the EU

All supplies indicated in Table 16 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 16 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Sites will receive kits of vials (for IV) or bottles (for Oral), which will be individually labeled in an unblinded fashion.

9.3 Clinical Supplies Disclosure

This trial is assessor blinded; therefore, the subject, the unblinded trial site personnel, the Sponsor and/or designee are not blinded. Study treatment is administered by unblinded personnel at the site (while the subject is hospitalized). Tedizolid phosphate (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

Participants whose treatment assignment has been unblinded by the investigator/delegate and/or nonstudy treating physician must be discontinued from study drug, but should continue to be monitored in the study. Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IRT system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IRT system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By providing documented informed consent, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all

applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in Section 12.1 - Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, MSD, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and

functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. MSD will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

12.2 Approximate Blood Volumes Drawn by Trial Visit and by Sample Types

It is recognized that pediatric centers reduce required blood volumes for standard clinical testing based on the size of the child, with centers generally suggesting a 1 mL draw for most standard clinical tests (blood culture, hematology with differential, and clinical chemistry panels), and a lower volume in neonates. For PK samples, 250 µL volumes are required per sample for Cohorts 1-3; while smaller volumes (100 µL per sample) are required for Cohort 4, with fewer samples collected. With this in mind, expected blood volumes for Cohorts 1-3 and for Cohort 4 are proposed below.

Table 17 Approximate Blood Volumes Drawn by Trial Visit and by Sample Types

Trial Visit:	Visits 1-2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	TOTAL
Blood Parameter	**Approximate Blood Volume (mL)**							
Cohorts 1, 2, and 3								
Hematology	1 mL	-	1 mL	-	1 mL	-	-	3 mL
Serum/Plasma Chemistry	1 mL	-	1 mL	-	1 mL	-	-	3 mL
Blood culture [a]	1 mL	-	1 mL[a]	-	1 mL[a]	-	-	3 mL
Plasma pharmacokinetics	0.5 mL	-	0.5 mL	-	-	-	-	1 mL
Expected Total (mL)	3.5 mL	-	3.5 mL	-	3 mL	-	-	**10 mL**
Cohort 4								
Hematology	0.5 mL	-	-	-	0.5 mL	-	-	1 mL
Serum/Plasma Chemistry	0.5 mL	-	-	-	0.5 mL	-	-	1 mL
Plasma pharmacokinetics	0.1 mL	-	0.2 mL	-	-	-	-	0.3 mL
Expected Total (mL)	1.1 mL	-	0.2 mL	-	1 mL	-	-	**2.3 mL**

a For Cohorts 1, 2, and 3, blood cultures are only collected at later visits if prior result was positive or if clinically indicated (not required to be collected for Cohort 4).

The total volume drawn for Cohorts 1, 2, and 3, in a scenario where blood cultures are performed at all required visits, is maximally 10 mL, which is approximately 3 mL blood per kg at the lowest allowable weight reasonably anticipated in this age range (3.2 kg).

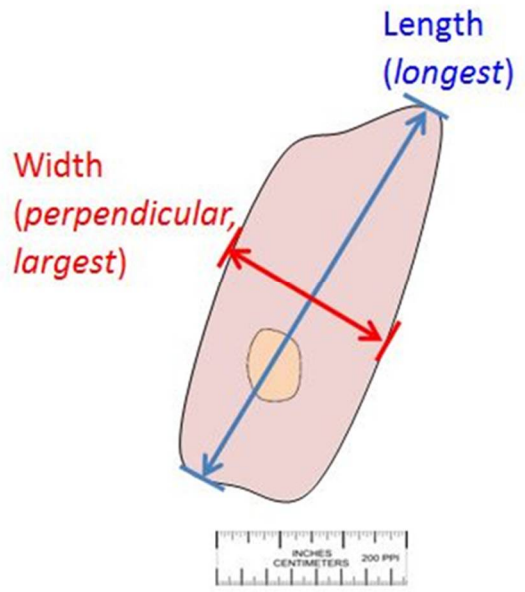
For neonates (Cohort 4), the total maximal volume is lower, commensurate with the lower expected weight range (down to 1 kg eligible for the study), likewise within 3 mL blood per kg of body weight for the smallest allowed neonate.

While larger volumes may be collected for laboratory testing in older subjects, no more than 3-4 mL blood per kg of body weight should be drawn during the course of this study, in accordance with safe limits proposed by WHO [8].

12.3 Site Instructions for Primary ABSSSI Site Measurement

1. Measurements of EEI, whichever is largest, should be performed along the *longest* dimension, regardless of the orientation with the axis of the body or limb. 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 (shown below) and document the measurement in the source document.

Measure the longest lesion dimension (length) regardless of the orientation to the body, and the longest width perpendicular to that length.


12.4 Signs and Symptoms of ABSSSI

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. Note: Induration, drainage, and fluctuance are only rated as present or absent.

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

	Absent	**Mild**	**Moderate**	**Severe**
Erythema	None	Pink	Red	Fiery red
Swelling/edema	None	Swelling just apparent on casual inspection (up to 2 mm of pitting)	Marked swelling (≤4 mm of pitting)	Maximal swelling (>4 mm of pitting)
Localized warmth	None	Slightly warm	Warm	Hot
Tenderness on palpation	None	Slight or mild tolerable discomfort on palpation	Uncomfortable with light palpation or pressure	Intolerable by even a mild stimulus such as sheet touching

12.5 Neurological 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. Tests that require verbal feedback (or verbal understanding of instructions) should be performed in verbal subjects only.

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

*Olfactory nerve assessment is optional.

12.6 Microbiological Sampling and Pathogen Determination

Appropriate specimens (aspirates, biopsy, deep swabs etc.; superficial swabs are not acceptable) of the primary ABSSSI site and blood will be collected at various time points (see Section 6.0). 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 ABSSSI site should be sent to the site's local laboratory for Gram stain and culture. Blood samples should be sent to the site's local laboratory for culture (Gram stain optional). Isolates should be identified using the local laboratory's usual procedures. All unique organisms from the ABSSSI site and/or blood samples will be stored and sent to the MSD designated central laboratory for confirmation of identification and susceptibility testing.

Backup samples of all organisms isolated from the ABSSSI 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 MSD to discard them or ship them to MSD 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 eCRF.

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
- ≥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:

Always a pathogen: If the organism was isolated from the culture of the ABSSSI, 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 β–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 ≥ 2 pathogens or with a pathogen not on the "Monomicrobial Infection" list will be reviewed on a case-by-case basis.

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

   S. saprophyticus

   Corynebacterium spp.

   S. epidermidis

   Bacillus spp.

   Diphtheroids

   Micrococci

   Candida spp., Aspergillus spp., or other fungi

2. 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 MSD. If needed, subject clinical (e.g., type of infection, type of specimen, subject underlying conditions, etc.) and microbiological information (e.g., Gram stain, etc.) will be used to assist in determining if the isolate is a pathogen. All organisms isolated from a blood culture and all gram-negative organisms will be reviewed by MSD to determine if the organism is a pathogen.

12.7 Pain Evaluation

Verbal Subjects: WONG-BAKER FACES PAIN RATING SCALE

For verbal subjects, pain will be evaluated using the Wong-Baker FACES Pain Rating Scale throughout the study (Figure 2) [9]. 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 FACES tool. 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 eCRF.

Figure 2 Pain Assessment Scale

Nonverbal Subjects: FLACC BEHAVIORAL PAIN SCALE

For nonverbal subjects, pain will be evaluated using the FLACC Behavioral Pain Scale throughout the study (Table 18, Table 19).

Table 18 Nonverbal Subjects: FLACC Behavioral Pain Scale

Categories	Scoring		
	0	**1**	**2**
Face	No particular expression or smile	Occasional grimace or frown; withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams, or sobs; frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort

Source: Modified from [9].

HOW TO USE FLACC:

In patients who are awake: observe for 1 to 5 minutes or longer. Observe legs and body uncovered. Reposition patient or observe activity. Assess body for tenseness and tone. Initiate consoling interventions if needed.

In patients who are asleep: observe for 5 minutes or longer. Observe body and legs uncovered. If possible, reposition the patient. Touch the body and assess for tenseness and tone.

Table 19 FLACC Behavioral Scale

Face

➢ Score 0 if the patient has a relaxed face, makes eye contact, shows interest in surroundings.

➢ Score 1 if the patient has a worried facial expression, with eyebrows lowered, eyes partially closed, cheeks raised, mouth pursed.

➢ Score 2 if the patient has deep furrows in the forehead, closed eyes, an open mouth, deep lines around nose and lips.

Legs

➢ Score 0 if the muscle tone and motion in the limbs are normal.

➢ Score 1 if patient has increased tone, rigidity, or tension; if there is intermittent flexion or extension of the limbs.

➢ Score 2 if patient has hypertonicity, the legs are pulled tight, there is exaggerated flexion or extension of the limbs, tremors.

Activity

➢ Score 0 if the patient moves easily and freely, normal activity or restrictions.

➢ Score 1 if the patient shifts positions, appears hesitant to move, demonstrates guarding, a tense torso, pressure on a body part.

➢ Score 2 if the patient is in a fixed position, rocking; demonstrates side-to-side head movement or rubbing of a body part.

Cry

➢ Score 0 if the patient has no cry or moan, awake or asleep.

➢ Score 1 if the patient has occasional moans, cries, whimpers, sighs.

➢ Score 2 if the patient has frequent or continuous moans, cries, grunts.

Consolability

➢ Score 0 if the patient is calm and does not require consoling.

➢ Score 1 if the patient responds to comfort by touching or talking in 30 seconds to 1 minute.

➢ Score 2 if the patient requires constant comforting or is inconsolable

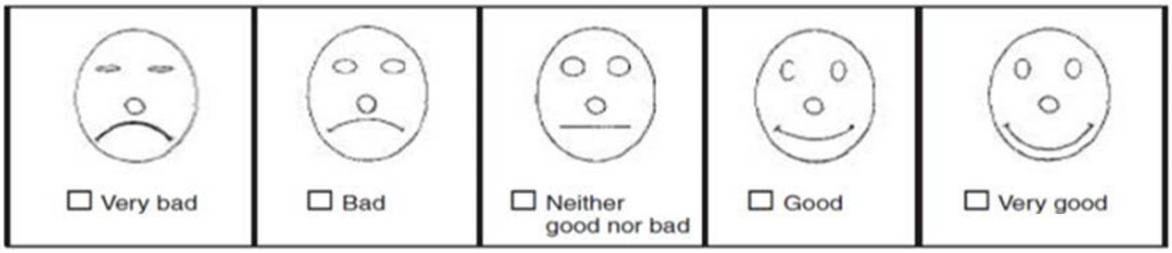
Source: [10]

12.8 Acceptability and Palatability Assessment

Palatability will be evaluated **one time only** using a 5-point hedonic scale (Figure 3) as well as a series of acceptability questions within 30 minutes of the first oral administration. This should be queried of the subject, for verbal subjects, but can be assessed by the nurse/healthcare provider or parent/caregiver witnessing the dosing, for nonverbal subjects.

Figure 3 Palatability Scale

1. Please mark the box of one picture below to show how you/the child feels about the taste of the medication:



2. Please mark one box below to identify the person entering the responses on the questionnaire.
   - ☐ Reported by the patient
   - ☐ Observed by a nurse
   - ☐ Observed by a parent/primary caregiver
   - ☐ Observed by another health care provider (e.g.: physician, medical assistant or nursing assistant caring for the patient)

3. Please indicate if you/the child had any of the following problems when taking the medication by mouth:

a. Refusing	☐ Yes	☐ No
b. Spitting Out	☐ Yes	☐ No
c. Vomiting or Spitting Up	☐ Yes	☐ No
d. Gagging	☐ Yes	☐ No
e. Other, specify	☐ Yes	☐ No _____

4. Are there any other comments related to the taste of the medication? ☐ Yes ☐ No
   Specify comments: _____

12.9 Examples of Prohibited Concomitant Medications

The examples of prohibited concomitant medications in Table 20 are not all-inclusive and should be used as a guide for exclusion from the protocol. Receipt of these medications is prohibited in the 2 weeks prior to study through the EOT Visit.

Table 20 Examples of Prohibited Concomitant Medications

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

Note: For breastfed subjects, consideration should be given to any prohibited medications taken by the mother, with appropriate steps taken to avoid exposure to the subject. See also Section 5.1.3.

12.10 Abbreviations

The following terms may be used interchangeably within the document:

- Subject and participant
- Trial and study

Abbreviation or Term	Explanation
ABSSSI	acute bacterial skin and skin structure infections
AE	adverse event
ALT	alanine transaminase
AMA	American Medical Association
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	AUC from time zero extrapolated to infinity
BCRP	breast cancer resistance protein
BID	twice a day
CA	community-acquired
CE-TOC	clinically evaluable at test-of-cure
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
COVID-19	coronavirus disease 2019
CSR	clinical study report
cSSTI	complicated skin and soft tissue infection
DMC	Data Monitoring Committee
EC	exclusion criteria
ECG	electrocardiogram
ECI	events of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
EEI	erythema, edema, and/or induration
EMA	European Medicines Agency
EOC	Executive Oversight Committee

Abbreviation or Term	Explanation
EOT	End of Therapy
ERC	Ethics Review Committee
EU	European Union
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act
FDAMA	FDA Modernization Act
FLACC	Face, Legs, Activity, Cry, Consolability (behavioral pain rating scale)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
HgB	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC	inclusion criteria
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	International Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	intent to treat
IV	intravenous
LAR	legally acceptable representative
LFU	Late Follow-up
MAO	monoamine oxidase
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MITT	microbiological intent to treat
MRSA	methicillin-resistant *Staphylococcus aureus*
OTC	over the counter
PD	pharmacodynamic
PIP	Pediatric Investigational Plan
PK	pharmacokinetic(s)
PO	oral

Abbreviation or Term	Explanation
PSP	Pediatric Study Plan
PTC	peptidyl transferase center
q12h	twice daily
QD	once daily
SAE	serious adverse event
SMQ	standard MedDRA query
SOP	standard operating procedure
sSAP	supplemental statistical analysis plan
SSI	surgical site infection
SSTI	skin and soft tissue infections
TEAE	treatment-emergent adverse event
TOC	test-of-cure
US	United States
WBC	white blood cell
WHO	World Health Organization

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	