Official Protocol Title:	A Phase 1, Single- and Multiple-Dose Safety and Pharmacokinetic Study of Oral and IV Tedizolid Phosphate (MK-1986) in Inpatients Under 2 Years Old
NCT number:	NCT03217565
Document Date:	06-Jul-2022

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TITLE:

A Phase 1, Single- and Multiple-Dose Safety and Pharmacokinetic Study of Oral and IV Tedizolid Phosphate (MK-1986) in Inpatients Under 2 Years Old

IND NUMBER: 125076 and 106307
EudraCT NUMBER: 2017-000953-38
NCT NUMBER: 03217565

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	06-JUL-2022	To remove the dependency of enrollment of the second cohorts of Groups 2 and 3 on the availability of safety/tolerability data from Study MK-1986-018.
Amendment 04	01-JUN-2021	To clarify that participants can receive the oral suspension dose via feeding tube.
Amendment 03 (Ukraine only)	16-JAN-2020	To indicate that neither Ukraine nor Norway will enroll subjects in Groups 3 and 6 (preterm neonates).
Amendment 02	11-OCT-2019	To update the dose levels following the first interim analysis and to convert the second IV cohort of each neonatal group to receive multiple (not single) doses.
Amendment 01	13-SEP-2018	To ensure an adequate distribution of age and weight among subjects aged 28 days to <24 months, particularly among subjects aged 28 days to <6 months.
Original Protocol	23-JUN-2016	Not applicable

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

To remove the dependency of enrollment of the second cohorts of Groups 2 and 3 on the availability of safety/tolerability data from Study MK-1986-018.

Section Number	Section Title	Description of Change	Rationale
2.1	Trial Design	Removed dependency of enrollment of the second cohorts of Groups 2 and 3 on the availability of safety/tolerability data from Study MK-1986-018.	This contingency was initially in place to ensure that there was an understanding of the potential risks in neonates based on dosing in older subjects prior to initiating multiple dosing in neonates. From the review of all the available safety data from completed and ongoing single- and multiple-dose studies in pediatric subjects from birth to <18 years of age, tedizolid phosphate is generally well tolerated with no new safety concerns identified in the pediatric population and no age-related trends in tolerability. Therefore, this contingency is being removed and multiple dosing of neonates will be allowed to proceed.

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.

Section Numbers	Section Titles	Description of Changes	Rationale
2.1	Trial Design	Changed all study design description text to future tense.	The trial design section should describe the plan; actual conduct and outcomes are described in Section 4, Background and Rationale.
4.2.2	Rationale for Dose Selection/Regimen/Modification	Added text to indicate that continuation at the initial planned dose levels were supported by interim analyses during the course of this study.	To clarify that the planned interim analyses during the course of the study have been conducted (and have supported continuation at the planned dose).
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 the pediatric population.
5.2	Trial Treatment(s)	The table of Trial Treatment (Table 2) was updated to add information for intervention type, dose formulation, unit dose strength, regimen, and sourcing.	To align with the Sponsor's current protocol standards.
Title Page Section 12.1 Throughout	Title Page Code of Conduct for Clinical Trials	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 12.1	Code of Conduct for Clinical Trials	Updates to the protocol template text.	To align with the current version of the Code of Conduct and other regulatory, ethical, and study governance requirements.

Section Numbers	Section Titles	Description of Changes	Rationale
Throughout Document		Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

1.0 TRIAL SUMMARY

Abbreviated Title	A Single- and Multiple-dose Study of Tedizolid Phosphate in Pediatric Subjects Aged <2 Years
Sponsor Product Identifiers	MK-1986 (tedizolid phosphate)
Trial Phase	Phase 1
Clinical Indication	Treatment or prophylaxis against gram-positive infections
Trial Type	Interventional
Type of control	Uncontrolled
Route of administration	Intravenous (Part A) and oral (as oral suspension; Part B)
Trial Blinding	Unblinded Open-label
Treatment Groups	Part A: Group 1 (N=10): • Cohort 1 (n=4-6): MK-1986 IV single-dose given to pediatric subjects aged 28 days to <6 months • Cohort 2 (n=4-6): MK-1986 IV single-dose given to pediatric subjects aged 6 months to <24 months Group 2 (N=10): • Cohort 1 (n=6): MK-1986 IV single-dose given to full-term neonates* aged birth to <28 days • Cohort 2 (n=4): MK-1986 IV multiple-dose (twice daily for 3 days) given to full-term neonates* aged birth to <28 days Group 3 (N=10): • Cohort 1 (n=6): MK-1986 IV single-dose given to preterm neonates† aged birth to <28 days • Cohort 2 (n=4): MK-1986 IV multiple-dose (twice daily for 3 days) given to preterm neonates† aged birth to <28 days Part B: Group 4 (N=4): MK-1986 oral suspension single-dose given to pediatric subjects aged 28 days to <24 months, Group 5 (N=4): MK-1986 oral suspension single-dose given to full-term neonates* aged birth to <28 days, and Group 6 (N=4): MK-1986 oral suspension single-dose given to preterm neonates† aged birth to <28 days In subjects who receive multiple-dose study medication, tedizolid phosphate will be administered twice daily for 3 days.

	* Full-term neonate is defined as an infant born ≥37th week of gestation. † Preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation
Number of trial subjects	Approximately 42 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 3 years from the time the documented informed consent is provided for the first subject until the last subject's last study-related phone call or visit. 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 approximately 18-20 days from the time the parent, guardian, or legally acceptable representative provides the documented informed consent form (ICF) through the final contact (Day 14). After a screening phase of ≤4 days, each subject will receive tedizolid phosphate as a single-dose or as multiple doses (twice daily for 3 days). After dosing is complete, each subject will be followed for 14 days for adverse events.

A list of abbreviations used in this document can be found in Section 12.4.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non-randomized, two-part, multisite, open-label trial to assess the safety and pharmacokinetics (PK) of tedizolid phosphate and its active metabolite tedizolid in hospitalized subjects (inpatients) aged <2 years who are receiving prophylaxis or treatment for a confirmed or suspected infection with gram-positive bacteria, to be conducted in conformance with Good Clinical Practices.

Safety and PK will be assessed following administration of tedizolid phosphate IV (Part A) or oral suspension (Part B) to pediatric inpatients aged 28 days (subjects may be preterm or full-term at birth) to <6 months, 6 months to <24 months, and 28 days to <24 months (Group 1 Cohort 1, Group 1 Cohort 2, and Group 4, respectively), full-term neonates aged birth to <28 days (Groups 2 and 5, respectively), and preterm neonates aged birth to <28 days (Groups 3 and 6, respectively). A full-term neonate is defined, in this study, as an infant born ≥37th week of gestation. A preterm neonate is defined, in this study, as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

Study progression to younger subjects will occur as follows: Group 1 Cohort 1 (IV, aged 28 days to <6 months) and Group 1 Cohort 2 (IV, aged 6 months to <24 months) will initiate enrollment first, at a dose of 3 mg/kg, based on the interim results of a separate PK and tolerability study in children aged 2 to <12 years, MK-1986-013 (TR701-120). To ensure adequate representation of age and weight within the 28 days to <24 months age range, a minimum of 2 subjects each will be enrolled into Group 1 Cohorts 1 and 2 prior to the first

interim assessment. After the first 5 subjects are enrolled in Group 1 (Cohorts 1 and 2 combined), an interim assessment of PK from this study (MK-1986-014) will be performed to determine whether the dose required adjustment.

After dose adjustment based on the first interim assessment, Group 1 Cohorts 1 and 2 will continue enrolling until complete; then Group 4 (aged 28 days to <2 years, receiving oral suspension) will enroll. In parallel, the first cohorts of Groups 2 and 3 (single-dose IV, full-term and preterm neonatal age groups) will begin enrollment at the planned starting dose of 3.0 mg/kg (body weight <10 kg) or 2.5 mg/kg (body weight 10 to <30 kg). After 6 subjects each are enrolled in the first cohorts of Groups 2 and 3, separate interim assessments will be performed for a potential dose adjustment. Enrollment of the second cohorts of Groups 2 and 3 (multiple-dose tedizolid phosphate) will occur only after these separate interim assessments.

Note, as of Amendment 05, these assessments have been completed, and enrollment of the second cohorts of Groups 2 and 3 (multiple-dose IV, full-term and preterm neonatal groups) will be initiated, supported by the safety profile observed across all age groups in studies MK-1986-014 and MK-1986-018.

Along with the second cohorts of Groups 2 and 3, Groups 5 and 6 will open for enrollment. Given the high bioavailability of tedizolid (approximately 90%) expected based on data from adults and older children, the oral suspension treatment will be administered at the dose selected based on the interim IV PK data. No interim analyses are planned for Part B (oral suspension) because of the small size of the oral groups.

Each of the IV groups (Group 1 [Cohorts 1 and 2 combined], Group 2 [Cohorts 1 and 2 combined], and Group 3 [Cohorts 1 and 2 combined]) will contain at least 10 subjects, with interleaved PK sampling such that data from all timepoints are obtained but no single subject provides more than 3 PK samples, to ensure total blood collection volume is within a safe range for the age group. Similarly, the oral groups (Groups 4, 5, and 6) will each have at least 4 subjects, again with interleaved PK sampling. Because of the relatively sparse nature of the sampling, subjects may be replaced if they are missing >1 PK sample (see Section 5.9).

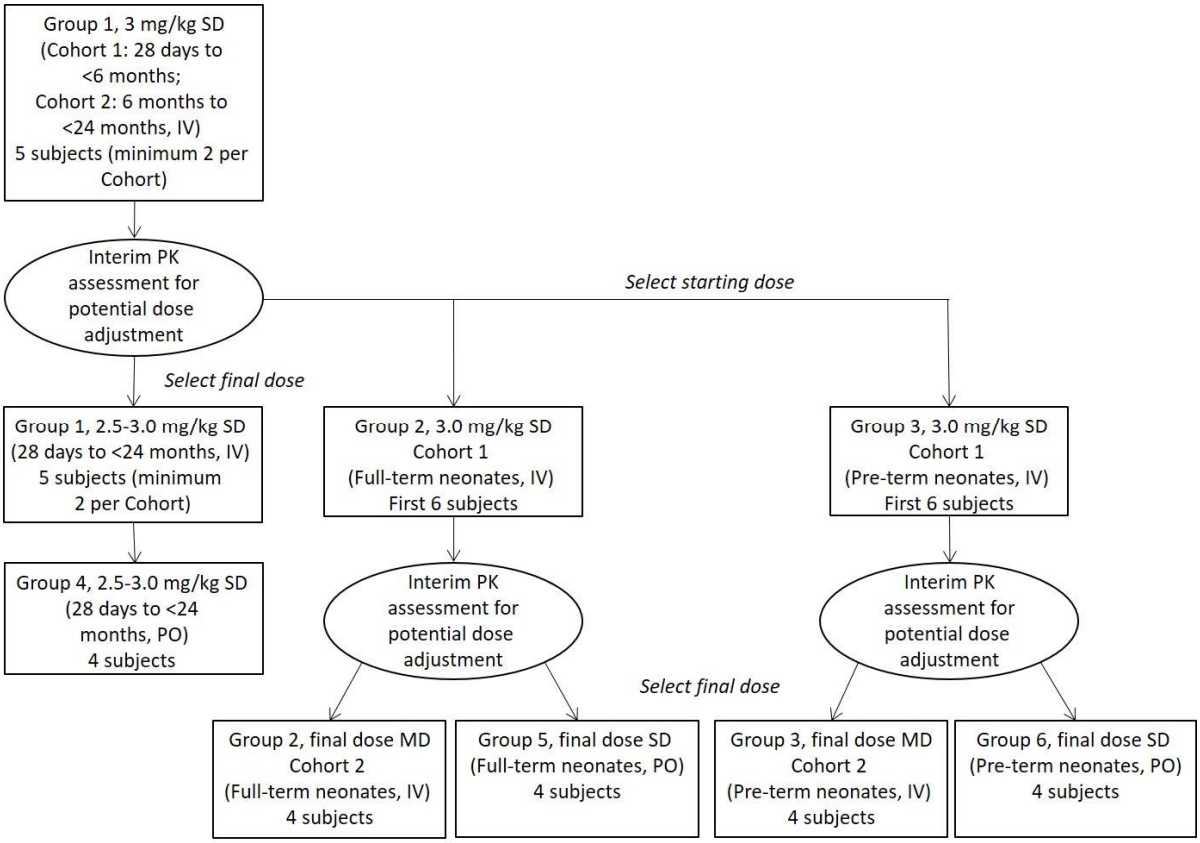
Further local restrictions on cohort opening may be applied based on country-specific requirements or site constraints.

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 Schematic of Study Design for Study MK-1986-014 (TR701-121)



IV=intravenously; MD=multiple-dose (twice daily for 3 days); PK=pharmacokinetics; PO=orally; SD=single-dose

Note: With the exception of the first 5 subjects in Group 1 (3 mg/kg single-dose), subjects in the study will receive body weight-based doses of tedizolid phosphate, as follows: <10 kg - 3.0 mg/kg tedizolid phosphate; 10 to <30 kg - 2.5 mg/kg tedizolid phosphate (see Section 5.2). This may be modified further after additional interim analyses.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Part A

1. Primary Objective**:** To describe the single-dose pharmacokinetics (PK) of IV tedizolid phosphate and its active metabolite, tedizolid, when administered to pediatric subjects, aged 28 days to <24 months (Group 1 [Cohorts 1 and 2 combined]), full-term neonates[a] aged birth to <28 days (Group 2), and preterm neonates[b] aged birth to <28 days (Group 3).

2. Primary Objective**:** To describe the multiple-dose PK of IV tedizolid phosphate and its active metabolite, tedizolid, when administered to full-term neonates[a] aged birth to <28 days (Group 2), and preterm neonates[b] aged birth to <28 days (Group 3).

Part B

3. Primary Objective**:** To describe the single-dose PK of tedizolid following oral suspension of tedizolid phosphate administration to pediatric subjects aged 28 days to <24 months (Group 4), full-term neonates[a] aged birth to <28 days (Group 5), and preterm neonates[b] aged birth to <28 days (Group 6).

[a] Full-term neonate is defined, in this study, as an infant born ≥37th week of gestation.

[b] Preterm neonate is defined, in this study, as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

3.2 Secondary Objective(s) & Hypothesis(es)

Part A

1. Secondary Objective**:** To evaluate the safety and tolerability of IV tedizolid phosphate administration in pediatric subjects aged 28 days to <24 months (Group 1 [Cohorts 1 and 2 combined]), full-term neonates[a] aged birth to <28 days (Group 2), and preterm neonates[b] aged birth to <28 days (Group 3).

Part B

2. Secondary Objective**:** To evaluate the safety and tolerability of oral suspension tedizolid phosphate administration in pediatric subjects aged 28 days to <24 months (Group 4), full-term neonates[a] aged birth to <28 days (Group 5), and preterm neonates[b] aged birth to <28 days (Group 6).

[a] Full-term neonate is defined, in this study, as an infant born ≥37th week of gestation.

[b] Preterm neonate is defined, in this study, as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

3.3 Exploratory Objectives

To describe the bioavailability of tedizolid following oral suspension tedizolid phosphate administration to pediatric subjects aged 28 days to <24 months (Group 4), full-term neonates[a] aged birth to <28 days (Group 5), and preterm neonates[b] aged birth to <28 days (Group 6).

[a] Full-term neonate is defined, in this study, as an infant born ≥37th week of gestation.

[b] Preterm neonate is defined, in this study, as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

Tedizolid phosphate (SIVEXTRO®, MK-1986) is a novel oxazolidinone prodrug antibiotic that is rapidly converted in vivo by phosphatases to the microbiologically active moiety tedizolid. Tedizolid is a protein synthesis inhibitor that interacts with the 50S subunit of the bacterial ribosome. Tedizolid has bacteriostatic activity against gram-positive bacteria including common skin pathogens Staphylococcus aureus (both methicillin-sensitive and –resistant strains) and Streptococcus pyogenes, less common species causing acute bacterial skin and skin structure infections (ABSSSI), S. anginosus-milleri group and Enterococcus faecalis, and other gram-positive aerobes and anaerobes. The tablet is highly (~90%) bioavailable after oral dosing in adults, and is provided in both IV and oral formulations. Following oral administration of a single 200 mg dose to healthy adults, maximal plasma concentrations of tedizolid (approximately 2 µg/mL) are achieved approximately 3 hours after dosing when fasted; Tmax is delayed by approximately 6 hours when tedizolid phosphate is dosed with a meal; however, the AUC is unaffected by administration with or without food. Conversion of the prodrug tedizolid phosphate to the active metabolite, tedizolid, is extremely rapid, with a half-life of 10 minutes. When the drug is dosed IV, exposure peaks at the end of the 60-minute infusion period. Systemic prodrug is rarely detectable after oral dosing. The terminal half-life of tedizolid elimination is 12 hours. Exposure is generally dose-proportional in humans.

Tedizolid phosphate is approved for the treatment of ABSSSI in adults in multiple regions, including the United States and European Union (EU), but its safety and effectiveness have not been established in children and adolescents.

4.1.2 Epidemiology, Microbiology, Pediatric Need

In both adults and children, ABSSSI accounts for a substantial proportion of emergency department visits and hospitalizations [1] [2]. However, an assessment of the exact incidence and prevalence of ABSSSI is difficult because of their variable presentation and short duration [1]. Across all pediatric age groups, ABSSSI can be extremely serious, including life-threatening and fatal infections.

Hospital-acquired methicillin-resistant *Staphylococcus aureus* (HA-MRSA) ABSSSIs tend to be associated with relatively high morbidity and mortality rates [3] [4]. The causative organisms for ABSSSI for both pediatric and adult populations are most commonly gram-positive bacteria including *S. aureus*, Group A streptococci, and enterococcus species [1]. Community-acquired MRSA (CA-MRSA) has become 1 of the most common causes of ABSSSI in both children and adults in the past decade [2] [5], particularly in the United States (US), but now increasingly in Europe as well.

New therapeutic options with activity against resistant pathogens remain an ongoing need in both the adult and pediatric populations.

4.1.3 Pediatric Age Subsets

Among pediatric groups, ABSSSIs are seen from premature infants to teenagers, without predilection for a particular age subset. The profile of causative ABSSSI pathogens is the same across pediatric age subsets without important differences from adult infection, with the

exception that in neonates and premature infants, MRSA infections tend to involve HA-MRSA strains rather than CA-MRSA.

4.1.4 Prior Preclinical and Clinical Experience

4.1.4.1 Preclinical Studies 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.

4.1.4.2 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 (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).

4.1.4.3 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_{∞} 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 pharmacokinetic 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 intravenous (IV) and/or oral 6-day 200 mg tedizolid phosphate (TZD) 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 adverse events overall and no changes to the safety profile identified for tedizolid phosphate.

A presentation of data from ongoing studies is included in Section 4.3 and in the Investigator's Brochure.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

This study will evaluate PK and safety following single- and multiple-dose administration of tedizolid phosphate in pediatric subjects aged birth to <24 months. Results will be used to inform doses for a safety and efficacy study (MK-1986-018) that includes young children (preterm neonates, full-term neonates, and infants/toddlers.) The study is part of an investigational plan that will evaluate the safety and efficacy of tedizolid phosphate in the treatment of children with ABSSSI. These studies are described in Table 1.

Table 1 Pediatric Studies

Study	Description
Completed	
Phase 1 PK TR701-111	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	Phase 3 study of IV to oral 6-day tedizolid phosphate compared with 10-day comparator in subjects 12 to <18 years with ABSSSI.
MK-1986-013 TR701-120	Phase 1, single-administration safety and PK study of oral and IV tedizolid phosphate in hospitalized subjects 2 to <12 years.
Ongoing	
MK-1986-018 TR701-128	Randomized, single-blind, safety and efficacy study of IV to oral tedizolid phosphate and comparator for ABSSSI in subjects birth to <12 years.
MK-1986-014 TR701-121	Phase 1, single- and multiple-dose safety and PK study of oral and IV tedizolid phosphate in inpatients under 2 years.

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

Results of Study TR701-111 established that exposure was similar in adults and adolescents and that tedizolid phosphate was well-tolerated with no clinically significant safety findings in 20 adolescent subjects. Results from this study enabled the initiation of studies in younger age groups.

Another study of safety and PK of single-dose tedizolid phosphate (oral suspension or IV) in subjects aged 2 to <12 years has since been completed (MK-1986-013 [TR701-120]). Safety and PK results from MK-1986-013 have been used to inform the appropriate dose for children over 2 years of age in an ongoing safety and efficacy study in children aged birth to <12 years (MK-1986-018), and provided information for selecting the initial dose for the present study, MK-1986-014.

The present study, MK-1986-014, is a safety and PK study of single-dose (oral or IV) or multiple-dose (IV only) administration of tedizolid phosphate in hospitalized subjects aged <2 years receiving prophylaxis for, or being treated for, a confirmed or suspected infection with gram-positive bacteria. This study was designed to rely on interim analysis of safety and PK results from the youngest age group (aged 2 to <6 years) in the PK and safety study (MK-1986-013 [TR701-120]) to determine the initial dose in younger children prior to enrollment, as described in Section 4.2.2. This study is designed to allow further adjustment of dose level based on interim analyses of PK and safety as the study continues.

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

4.2.2 Rationale for Dose Selection/Regimen/Modification

The proposed initial dose in the Initial Protocol for this study (5 mg/kg) was based on allometric scaling using existing adolescent and adult PK data, as no data were available at the time for children under 12 years of age. The expectation was that the dose would be confirmed or updated when such data became available, and prior to enrollment of this study. After finalization of the Initial Protocol, interim PK data in children aged 2 to <12 years became available from a single-dose PK study (MK-1986-013), and this has allowed expansion of the population PK model to younger age groups.

Area under the concentration versus time curve (AUC) is the appropriate PK parameter predicting efficacy for oxazolidinones. Prior to initiation of Study MK-1986-014, interim analysis from Study MK-1986-013 predicted that, in children aged 2 to 6 years, a dose of 3 mg/kg given twice daily would provide an AUC similar to that which has been shown to provide efficacy in adults with ABSSSI. Although tedizolid phosphate is delivered as a single daily dose to adults, this interim analysis indicated that the median C_{max} in subjects aged 2 to <6 years who received a 1-hour IV infusion of tedizolid phosphate 6 mg/kg in Study MK-1986-013 was approximately 3.75-fold higher than that in adults with ABSSSI who received tedizolid 200 mg in model-predicted Phase 2 and Phase 3 studies. Thus, the single tedizolid phosphate dose in the present study was modified to 3 mg/kg (with the intention that in multiple-dose studies in children aged <6 years, tedizolid phosphate will be administered twice daily) to achieve expected PK parameters, including distribution of maximal concentration (C_{max}), that are similar to those for which prior safety data in adults and adolescents are available.

Following enrollment of the first 5 subjects in Group 1, the pediatric population PK model was updated to include these data, as well as the PK data from the recently completed Studies MK-1986-012 and MK-1986-013 and an adolescent PK study, TR701-111. The updated model indicates that the weight-based tedizolid phosphate dose predicted to provide the closest approximation to adult exposure (as AUC and C_{max}) should be based on body weight range, with infants <10 kg receiving 3 mg/kg and children 10 to <30 kg receiving 2.5 mg/kg. Additional interim analyses of the neonatal single-dose IV cohorts have supported continuation of the study at these dose levels. In a multiple-dose setting, these doses would be given twice daily to achieve an AUC similar to that in adults at the approved dose, and likewise provide a high probability of target attainment (>99%) at the breakpoint MIC of 0.5 mg/L.

The addition of multiple-dose arms in this study allows for the collection of multiple-dose PK and safety data in full-term and preterm neonates, which will be difficult to obtain in treatment studies given the low incidence of ABSSSI in newborns.

Further dose modification may occur during the course of this study following review of additional interim data.

4.2.2.1 Rationale for the Use of Comparator/Placebo

Not applicable.

4.2.2.2 Starting Dose for This Trial

It was planned that subjects would receive a single dose of 3 mg/kg of tedizolid phosphate as either an IV infusion (Part A) or oral suspension (Part B). This dose was adjusted in Amendment 01, prior to the start of the study, from the single-dose of 5 mg/kg that was planned in the Initial Protocol. This dose adjustment was based on interim analyses of PK data from Study MK-1986-013 (see Section 4.2.2). Following the first interim analysis of the first 5 subjects enrolled in study MK-1986-014, the starting doses for the neonatal age groups have been further updated at Amendment 02 to 3.0 mg/kg (body weight <10 kg, which will span the entire neonatal age group).

4.2.2.3 Rationale for Dose Interval and Trial Design

This study will evaluate PK and safety following single- and multiple-dose administration of tedizolid phosphate in pediatric subjects aged birth to <24 months. Results will be used to inform doses for safety and efficacy studies in young children (preterm neonates, full-term neonates, and infants/toddlers). Age groups will be staggered (managed via interactive response technology [IRT]), with the subjects receiving the IV formulation in the older age group starting first, in order to provide the best predictive data for exposure in neonates prior to dosing. As noted in Section 4.2.2, the initial dose planned for this study was based on modeling and simulation using data from adolescents and from the now-completed PK and safety study, MK-1986-013, in subjects aged 2 to <12 years. This has been modified at Amendment 02 with the first interim analysis of data from the present study, MK-1986-014 (see Section 4.2.2). Further refinement of the dose may occur during the course of this study (eg, after the first 6 subjects in the IV arm for each age group) based on interim assessment of the accruing PK data. The dose may also be altered if a safety/tolerability issue is identified during the study that would necessitate dose reduction.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

No efficacy analysis will be performed. This is a study of the safety and PK of single- and multiple-dose administration of tedizolid phosphate in subjects aged birth to <24 months.

4.2.3.2 Safety Endpoints

There are no specific safety endpoints for this trial. Safety will be assessed through descriptive statistics within the Safety Analysis Set for each age group and dose cohort. Safety assessments will include adverse events, laboratory evaluations, and physical exams including vital signs. Adverse events of clinical interest for this protocol include clinically significant hematologic abnormalities, serotonin syndrome, and *Clostridium difficile* infection, in addition to drug-induced liver toxicity and overdose (which are events of clinical

interest for all MSD-sponsored studies). Myelosuppression and serotonin syndrome have been observed with linezolid, a drug in the same pharmaceutical class (oxazolidinone) as tedizolid, and these events are therefore considered potential risks for tedizolid phosphate. To date, clinical studies have not shown an increased risk for clinically significant hematologic abnormalities at the therapeutic dose and standard duration of treatment (6 days) of tedizolid phosphate. Likewise, monoamine oxidase (MAO) inhibition in the central nervous system has not been observed in vivo with tedizolid phosphate. MAO inhibition is responsible for sporadic cases of serotonin syndrome reported in postmarketing experience with linezolid when given in combination with certain serotonergic medications (such as selective serotonin reuptake inhibitors [SSRIs], among others). *C. difficile* infection can be triggered by nearly any antibiotic, and *C. difficile* infection is actively monitored in studies of tedizolid phosphate.

4.2.3.3 Pharmacokinetic Endpoints

The primary endpoint of the PK analysis is the AUC in each age group. Other standard PK parameter values (as described in Section 8.2.4.3 [CL or CL/F, Vd or Vd/F, C_{max}, T_{max}, $t_{½}$, and %BA]) will be calculated, as appropriate; however, as AUC is the PK parameter predicting efficacy for oxazolidinones, this is the most important parameter to inform the dose for later studies. Bioavailability of tedizolid following administration of tedizolid phosphate oral suspension (Part B) is an exploratory analysis.

4.2.3.4 Pharmacodynamic Endpoints

There are no pharmacodynamics endpoints for this trial.

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. Community-acquired MRSA (CA-MRSA) has become 1 of the most common causes of ABSSSI in both children and adults in the past 15 years [2] [5], particularly in the United States (US). 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, the limited availability of clinical data in pediatric populations, and the toxicity profile of currently available antibiotics that are 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.

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 4.1.4.3 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. These data support the safety of opening of MK-1986-014 in all age groups.

Unlike linezolid, tedizolid phosphate was not shown to be a monoamine oxidase inhibitor (MAOI) in vivo, and is therefore unlikely to increase the risk of serotonin syndrome. While tedizolid was a weak MAOI 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 MAOI and serotonergic medications were excluded (and they are therefore excluded in this study).

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 once daily treatment for certain age groups, a short course of therapy, and no dose adjustment between oral tablet/suspension and IV administration.

The safety and PK profile of tedizolid phosphate is similar in adults and adolescents, which suggests that the agent would be expected to provide similar efficacy in adolescent patients as in adult patients.

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 BCRP at the intestinal level, increasing plasma concentrations of BCRP substrates such as rosuvastatin, and the potential for adverse reactions. If possible, an interruption in the treatment of the coadministered 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, or irinotecan).

Thus, since tedizolid phosphate has already proven efficacious in adults for gram-positive infections, there is minimal risk with regard to the treatment of the underlying issue for the subjects in this study. Notably, subjects are required to be concomitantly receiving antibiotics

for their confirmed or suspected underlying infection (or for prophylaxis). No reliance is placed on the dose(s) of tedizolid phosphate to provide efficacious treatment.

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.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects who are medically stable inpatients, aged birth to <24 months, and who are receiving prophylaxis to prevent gram-positive bacterial infection or have a confirmed or suspected gram-positive bacterial infection and are receiving concurrent treatment with an antibiotic with gram-positive antibacterial activity 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. Be a male or female aged birth to <24 months.
2. Be hospitalized* and receiving prophylaxis for or have a confirmed or suspected infection with gram-positive bacteria and receiving concurrent antibiotic treatment with gram-positive antibacterial activity. The most recent dose of concurrent antibiotic treatment should be administered within 24 hours prior to randomization, except for concurrent long-acting antibiotics that are administered once (eg, dalbavancin, oritavancin).

   Note: This applies to all subjects, regardless of tedizolid phosphate treatment duration.
3. Be at least 1 kg in weight.
4. Be in stable condition as determined from medical history, physical examination, electrocardiogram (ECG [minimally 5-lead]; ECG not required for neonates), vital signs, and clinical laboratory evaluations.
5. Have no cardiac or electrocardiogram (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.
6. Have serum creatinine within 1.5 × upper limit of the reference range based on age.
7. Have parents willing to adhere to the prohibitions and restrictions specified in this protocol.
8. Have sufficient vascular access to receive trial drug (for subjects enrolled in Part A) and allow for blood draws required by the protocol.

9. Have consent: Parents or subjects' legally acceptable representative(s) provide documented informed consent indicating that they understand the purpose of and procedures required for the study and are willing to have their child participate in the study.
10. Be able to receive medication by mouth, for subjects to be dosed with oral suspension; dose administration via feeding tube is acceptable.

* It is acceptable to domicile the subject overnight at a clinical research unit if the subject is not otherwise planned to be admitted for his/her underlying disease.

5.1.3 Subject Exclusion Criteria

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

1. Has a history of seizures, other than febrile seizures, clinically significant cardiac arrhythmia or condition, moderate or severe renal impairment, or any physical condition that could interfere with the interpretation of the study results, as determined by the investigator.
2. Has any acute or chronic condition that, in the opinion of the investigator, would limit the subject's ability to complete and/or participate in this clinical study.
3. Has used rifampin within 14 days prior to dosing.**
4. Has used or will be using proton pump inhibitors, H2 blockers, or antacids (for subjects in Part B, ie, oral suspension dose) at any time from 24 hours prior to dosing through 24 hours after dosing.
5. Recent (3-month) history or current infection with viral hepatitis or other significant hepatic disease.
6. Has a history of drug allergy or hypersensitivity to oxazolidinones.
7. Has had significant blood loss (≥5% of total blood volume) for Groups 2, 3, 5, and 6 and significant blood loss within 4 weeks for Groups 1 and 4 before the Screening Visit. Total blood volume can be estimated as 80 mL per kg of body weight.
8. Need for oral administration of methotrexate, topotecan, irinotecan or rosuvastatin, during administration of oral study drug. (Administration during the follow-up period is allowed, as is administration during treatment with IV study drug.) **
9. Use of MAOIs or serotonergic agents including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin 5-hydroxytryptamine receptor agonists (triptans), meperidine, or buspirone within 14 days prior to study, or planned use while on study. See Section 12.3 for examples.**
10. Has received another investigational product within the 30 days prior to enrollment.
11. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

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

5.2 Trial Treatment(s)

It is planned that all subjects will receive a weight-based dose, selected based on body weight band, of tedizolid phosphate as either an IV infusion (Part A) or an oral suspension (Part B). The treatment(s) to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatment

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Part A	Experimental	Tedizolid phosphate (MK-1986)	Drug	Solution for infusion	Refer to product labeling	Body weight <10 kg: 3 mg/kg Body weight 10 to <30 kg: 2.5 mg/kg	IV	Single dose (Group 1, and cohort 1 of Groups 2, 3) Twice daily for 3 days (Cohort 2 of Groups 2, 3)	Test product	IMP	Central
Part B	Experimental	Tedizolid phosphate (MK-1986)	Drug	Oral Suspension	20 mg/mL	Body weight <10 kg: 3 mg/kg Body weight 10 to <30 kg: 2.5 mg/kg	Oral	Single dose (Groups 4, 5, 6)	Test product	IMP	Central

EEA =European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP 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 and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Note: Dose level is the same regardless of route. Dose may be further adjusted within this study based on data from enrolled subjects.

A single dose or multiple doses (twice daily for 3 days) of tedizolid phosphate will be administered to subjects after antimicrobial administration with a non-study antibiotic has been initiated for prophylaxis or for treatment of a presumed or confirmed gram-positive infection. The most recent dose of concurrent antibiotic treatment should be administered within 24 hours prior to randomization, except for concurrent long-acting antibiotics that are administered once (eg, dalbavancin, oritavancin).

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/Modification

5.2.1.1 Dose Selection (Preparation)

Tedizolid phosphate will be administered as single or multiple doses of 3.0 mg/kg or 2.5 mg/kg (with possible adjustment based on interim data from this study). Instructions for preparation of the IV solutions or oral suspensions will be provided in the Pharmacy Manual.

5.2.1.1.1 Intravenous Tedizolid Phosphate

Flush the IV line before and after study drug administration, per standard of care. No other IV therapy should be administered concurrently with the study drug.

A detailed method for preparation of the IV dosing solution is provided in the Pharmacy Manual.

Infuse the solution for injection at a rate to deliver the desired dose in 60±10 minutes.

Dose, allowable volumes, and infusion rate required are provided in the Pharmacy Manual. Record start and stop times in the source documents and electronic case report forms (e-CRFs). Monitor the subject for at least 30 minutes post-infusion.

5.2.1.1.2 Oral Tedizolid Phosphate

Oral tedizolid phosphate may be administered with or without food, but timeframe of the most recent meal must be recorded.

The target dose for administration of the oral suspension is based on body weight using the following formula:

$$\text{Target dose (mg/kg)} \times \text{body weight (kg)} = \text{dose required (mg)}$$

$$\text{Dose required (mg)/suspension concentration (mg/mL)} = \text{target volume (mL)}$$

Calculations of volume required are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Interim PK data will be reviewed after the completion of the first 6 subjects treated with IV therapy in Group 2 and 3. The dose may be adjusted to ensure exposure in this study is similar to that observed in adults.

5.2.2 Timing of Dose Administration

For subjects who receive single-dose tedizolid phosphate, dosing is unrestricted with respect to time. For oral dosing, the timeframe of the most recent meal must be recorded (see Section 5.2.1.1.2). For subjects who receive multiple-dose tedizolid phosphate, dosing is once every 12 hours ±1 hour.

5.2.3 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

During the course of the study, subjects will be assigned non-randomly to one of 2 different treatment routes (IV or orally) and to a specific PK sampling scheme. Treatment allocation will be controlled, and the PK sampling scheme will be assigned via IRT.

After the documented informed consent form is provided by the parent/guardian/LAR and study eligibility is confirmed, designated site study staff will obtain the subject's treatment allocation number and trial drug assignment from a computer-generated allocation code via IRT. Subjects enrolled in the study will be assigned the treatment and PK sampling scheme corresponding to the next available allocation number in the computer-generated schedule.

Treatment allocation will occur centrally using IRT. There are 6 treatment Groups (Group 1 is split into Cohorts 1 and 2 for the purposes of enrollment only). Within each Group, subjects will be assigned to one of two PK sampling schema, as described in Section 7.1.3.2.2. Subjects will be assigned non-randomly to tedizolid phosphate IV or oral suspension as follows:

Group 1 (N=10):

- Cohort 1 (n=4-6): MK-1986 IV single-dose given to pediatric subjects aged 28 days to <6 months.
- Cohort 2 (n=4-6): MK-1986 IV single-dose given to pediatric subjects aged 6 months to <24 months.

Group 2 (N=10):

- Cohort 1 (n=6): MK-1986 IV single-dose given to full-term neonates* aged birth to <28 days
- Cohort 2 (n=4): MK-1986 IV multiple-dose (twice daily for 3 days) given to full-term neonates* aged birth to <28 days

Group 3 (N=10):

- Cohort 1 (n=6): MK-1986 IV single-dose given to preterm neonates† aged birth to <28 days
- Cohort 2 (n=4): MK-1986 IV multiple-dose (twice daily for 3 days) given to preterm neonates† aged birth to <28 days

Group 4 (N=4): MK-1986 oral suspension single-dose given to pediatric subjects aged 28 days to <24 months,

Group 5 (N=4): MK-1986 oral suspension single-dose given to full-term neonates* aged birth to <28 days, and

Group 6 (N=4): MK-1986 oral suspension single-dose given to preterm neonates† aged birth to <28 days.

In subjects who receive multiple-dose study medication, tedizolid phosphate will be administered twice daily for 3 days.

Further local restrictions on cohort opening may be applied based on country-specific requirements or site constraints.

* Full-term neonate is defined as an infant born ≥37th week of gestation.

† Preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

5.4 Stratification

Treatment allocation will be stratified according to age.

5.5 Concomitant Medications/Vaccinations (Allowed & 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’s legally acceptable representative.

Prohibited concomitant medications for all Groups include the following:

- Rifampin
- BCRP substrates if given orally (topotecan, irinotecan, methotrexate, and rosuvastatin), for children receiving oral study medication
- MAOIs or serotonergic agents including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin 5-hydroxytryptamine receptor agonists (triptans), meperidine, or buspirone (see Section 12.3)

In addition, for subjects receiving oral suspension (Part B), proton pump inhibitors, H2 blockers, and antacid use are prohibited.

Note: Breastfed infants should be excluded if the mother is receiving any excluded medication, with the exceptions of proton pump inhibitors, H2 blockers, and antacids.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

There are no dietary or activity restrictions in this trial, except for oral dosing, timeframe of the most recent meal must be recorded (see Section 5.2.1.1.2).

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 7.1.5.3 – 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

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.3 – 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

If a subject discontinues from the trial or is missing >1 PK sample, a replacement subject may be enrolled if deemed appropriate by the Sponsor. The replacement subject will generally receive the same treatment and PK sampling sequence (as appropriate) as the subject being replaced. The replacement subject will be assigned a unique allocation number via IRT.

5.10 Beginning and End of the Trial

The overall trial begins when documented informed consent is provided for the first subject. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. 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	Treatment		Post-treatment
Visit Number/Title:	1 Screening	2 Allocation & Treatment	3 Day 2-3 Visit	Follow-up Telephone Contact[a]
Scheduled Day (single-dose)	-3 to 1[b]	1	2	14
Scheduled Day (multiple-dose)	-3 to 1[b]	1	2 – 3[c]	17
Scheduling Window (Days):				14-21
Administrative Procedures				
Informed Consent (before any trial-related procedures/assessments)	X			
Inclusion/Exclusion Criteria	X			
Subject Identification Card	X	X		
Medical History	X			
Prior and Concomitant Medication Review	X	X	X	X
Treatment Allocation		X		
Tedizolid Phosphate (MK-1986) Administration[d]		X	X[c]	
Clinical Procedures/Assessments				
Full Physical Examination	X			
Directed Physical Examination		X	X	
Height	X			
Weight	X			
Electrocardiogram (5-, 12-, or 15-lead)[e]	X			
Vital Signs (respiratory rate, BP, HR, temperature)[f,g]	X	X	X	
Adverse Events Monitoring	X	X	X	X

Trial Period:	Screening	Treatment		Post-treatment
Visit Number/Title:	1 Screening	2 Allocation & Treatment	3 Day 2-3 Visit	Follow-up Telephone Contact[a]
Scheduled Day (single-dose)	-3 to 1[b]	1	2	14
Scheduled Day (multiple-dose)	-3 to 1[b]	1	2 – 3[c]	17
Scheduling Window (Days):				14-21
Laboratory Procedures/Assessments				
Hematology Laboratory Tests[h]	X		X	
Blood Chemistry Laboratory Tests[h]	X		X	
Blood Samples for PK Analysis[i]		X[i]	X[i]	
Urinalysis	X			

Abbreviations: AE=adverse event; BP=blood pressure; ECG=electrocardiogram; HR=heart rate; IV=intravenous; PK=pharmacokinetics

a. The Post-treatment Follow-up Contact should be conducted in person if there are ongoing adverse events or clinically important laboratory abnormalities that require follow-up.
b. Screening procedures may be completed on Day 1. The screening window is up to 3 calendar days prior to treatment allocation.
c. Subjects assigned to receive multiple doses of IV tedizolid phosphate will receive study drug on Days 2 and 3. Study medication (single- or multiple-dose) will be dispensed once only from IRT. For multiple-dose subjects, the only study procedure on Day 2 is administration of study drug; all clinical and laboratory study procedures specified in the Trial Flow Chart (eg, hematology, chemistry, etc.) and administration of study drug should be performed on Day 3.
d. Subjects will be administered tedizolid phosphate as an IV infusion (Part A) or oral suspension (Part B). See Section 5.2 for more detail. Both oral and IV trial drug may be administered with or without food; for oral dosing, the timeframe of the most recent meal except parenteral feeding (within 24 hours) must be recorded.
e. Subjects will rest 10 minutes prior to ECG recordings at Screening; prestudy ECG (minimum 5-lead ECG) may be used if it was performed and documented within 1 month prior to enrollment. ECG is not required for neonates, but available data should be collected and reviewed.
f. Vital signs (including temperature (oral, tympanic, temporal, or rectal), respiratory rate, and resting blood pressure and pulse) will be measured at the Screening Visit, predose, and approximately 24 hours postdose.
g. Blood pressure and pulse only; obtained immediately prior to the first dose and at 1 hour after the first dose (relative to the start of infusion for IV administration). Obtain BP postdose with the same equipment and same position that were used for the baseline/predose measurement.
h. If blood tests (chemistry and hematology) have been conducted at the local laboratory within 7 days prior to allocation, they may be used (ie, they do not need to be repeated at screening for the purpose of the study). For subjects who receive single-dose tedizolid phosphate, blood for postdose chemistry and hematology should be collected any time on Day 2. For subjects who receive multiple-dose tedizolid phosphate, blood for postdose chemistry and hematology should be collected any time on Day 3.

i. PK samples will be interleaved across subjects so that each subject provides 3 PK samples. In Part A, blood samples for analysis of tedizolid phosphate and tedizolid will be collected at the following timepoints, depending on the assigned collection scheme: single-dose subjects - immediately after the end of the 1-hour infusion, and at 1.5, 3, 6, 12, and 24 hours after the start of infusion; multiple-dose subjects – Day 3 at 12 hours after start of the 4th dose infusion (prior to start of the 5th dose infusion), at end of infusion (5th dose) and 1.5, 3, 6, and 12 hours after start of the 5th dose infusion. In Part B, blood samples for analysis of tedizolid phosphate and tedizolid will be collected at the following timepoints, depending on the assigned collection scheme: 1, 3, 5, 8, 12, and 24 hours postdose. See Section 7.1.3.2.2 for details of interleaved collection. PK samples will not be collected from subjects receiving oral suspension who vomit during and/or within 90 minutes after administration of a dose.

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 be obtained from the subject's legally acceptable representative. 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

The investigator or qualified designee must obtain documented informed consent from each potential subject's legally acceptable representative prior to participating in a 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 qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent given by the subject's legally acceptable representative must be documented on a consent form.

A copy of the signed and dated consent form should be given to the subject's legally acceptable representative before that subject's participation in the trial.

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

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent 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 for the trial.

7.1.1.3 Subject Identification Card

The legally acceptable representative for each subject will be given a Subject Identification Card identifying the subject as a participant 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 legally acceptable representative for each subject with a Subject Identification Card immediately after documented informed consent is provided. 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 history will be obtained by the Investigator or qualified designee.

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, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before first dose of trial medication.

7.1.1.5.2 Concomitant Medications

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

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.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

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 allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. This will occur after consent is obtained, and confirmation of study eligibility (Section 5.3). 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

Interruptions from the protocol-specified procedures require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of each dose of trial medication will be witnessed by the investigator and/or trial staff and the time and date will be recorded in the Subject's e-CRF.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

Physical examinations will be conducted as per the trial flowchart. All physical examinations will include height and weight (at Screening), and vital signs (blood pressure [BP], heart rate [HR], respiratory rate, and temperature [oral, tympanic, temporal, or rectal]).

Note: a 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 Electrocardiogram

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

*ECG is not required for neonates, but available ECG data should be reviewed.

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/tissue to be drawn/collected over the course of the trial (from pretrial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Laboratory Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 3.

Table 3 Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**
Hematocrit	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Glucose
Platelet count	Alanine aminotransferase (ALT)	Protein
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity
Neutrophils (%, absolute)	Bicarbonate	Microscopic examination, if abnormal results are noted
Lymphocytes (%, absolute)	Calcium	pH
Monocytes (%, absolute)	Chloride	Bilirubin
Eosinophils (%, absolute)	Cholesterol[a]	Ketones
Basophils (%, absolute)	Creatinine	Urobilinogen
Bands (%, absolute)	Gamma-glutamyl transpeptidase[a]	
	Glucose	
	Phosphorus[a]	
	Potassium	
	Sodium	
	Total bilirubin	
	Direct bilirubin, if total bilirubin is elevated above the upper limit of normal	
	Indirect bilirubin[a]	
	Total protein	
	Uric acid[a]	
	Blood urea nitrogen	

WBC=white blood cell

[a] Not required, but will be collected if analyzed per local standard of care.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 Assessment

Plasma samples will be analyzed for concentrations of tedizolid phosphate and its active metabolite, tedizolid. For Groups 1-3 (receiving IV treatment), values for the individual PK parameters outlined below will be calculated for subjects with all postdose samples collected, based on the individual plasma concentration and actual sampling times. A naïve-pooled approach may also be used for Groups 1-3. For Groups 4-6 (receiving oral treatment), only a naïve-pooled approach will be used to determine the PK for each cohort (see Section 8.1.1.2 for details). In the naïve-pooled approach, mean concentrations at each of the timepoints will be calculated based on available data to construct one concentration-time profile. The mean profile will then be used to determine the PK parameter values for each oral cohort. PK parameter values for tedizolid and tedizolid phosphate including the following will be determined as appropriate:

- C_{max}
- t_{max}
- AUC
- $t_{½}$
- CL/F and CL
- Vd

Bioavailability (F) of tedizolid in each age group will be calculated as the ratio of the AUC (IV) to AUC (oral).

7.1.3.2.2 Samples

In Part A, blood samples for analysis of tedizolid phosphate and tedizolid will be collected at the following timepoints (Figure 2 or Figure 3) for subjects allocated to 1 of 2 collection schemes:

Subjects who receive single-dose tedizolid phosphate IV (shown graphically in Figure 2):

1. immediately after the end of the 1-hour infusion, and at 3 and 12 hours after the start of infusion

OR

2. at 1.5, 6, and 24 hours after the start of infusion

Subjects who receive multiple-dose tedizolid phosphate IV (shown graphically in Figure 3):

1. Day 3 at end of infusion (5^{th} dose), 3 hours after the start of the 5^{th} infusion, and 12 hours after the start of the 5^{th} infusion (prior to 6^{th} dose)

OR

2. Day 3 at 12 hours after the start of the 4^{th} infusion (prior to 5^{th} dose), 1.5 hours after the start of the 5^{th} infusion, and 6 hours after the start of the 5^{th} infusion

In Part B, blood samples for analysis of tedizolid phosphate and tedizolid will be collected at the following timepoints (Figure 4) for subjects allocated to 1 of 2 collection schemes:

Subjects who receive single-dose tedizolid phosphate oral suspension (shown graphically in Figure 4):

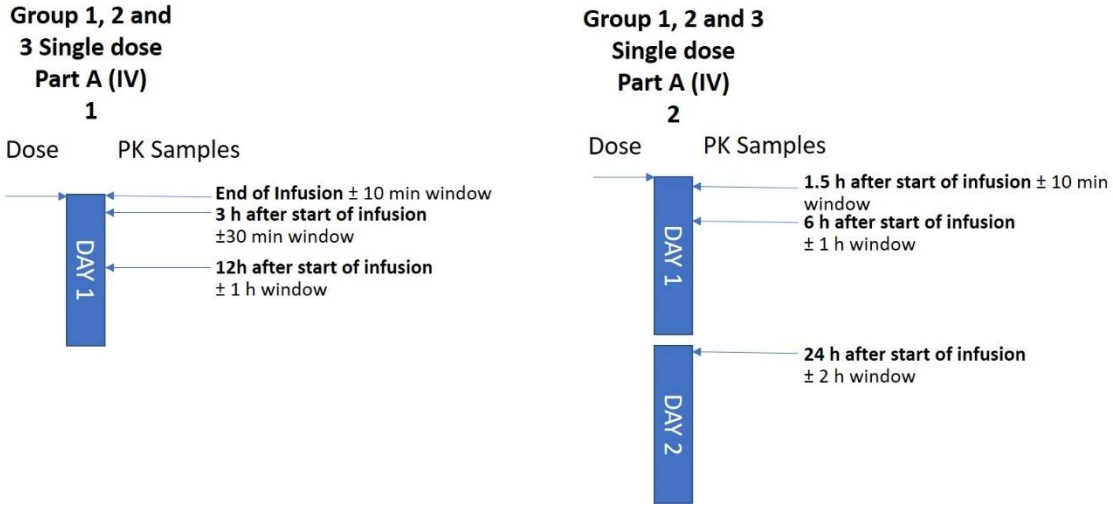
1. at 1, 5, and 12 hours postdose

OR

2. at 3, 8, and 24 hours postdose

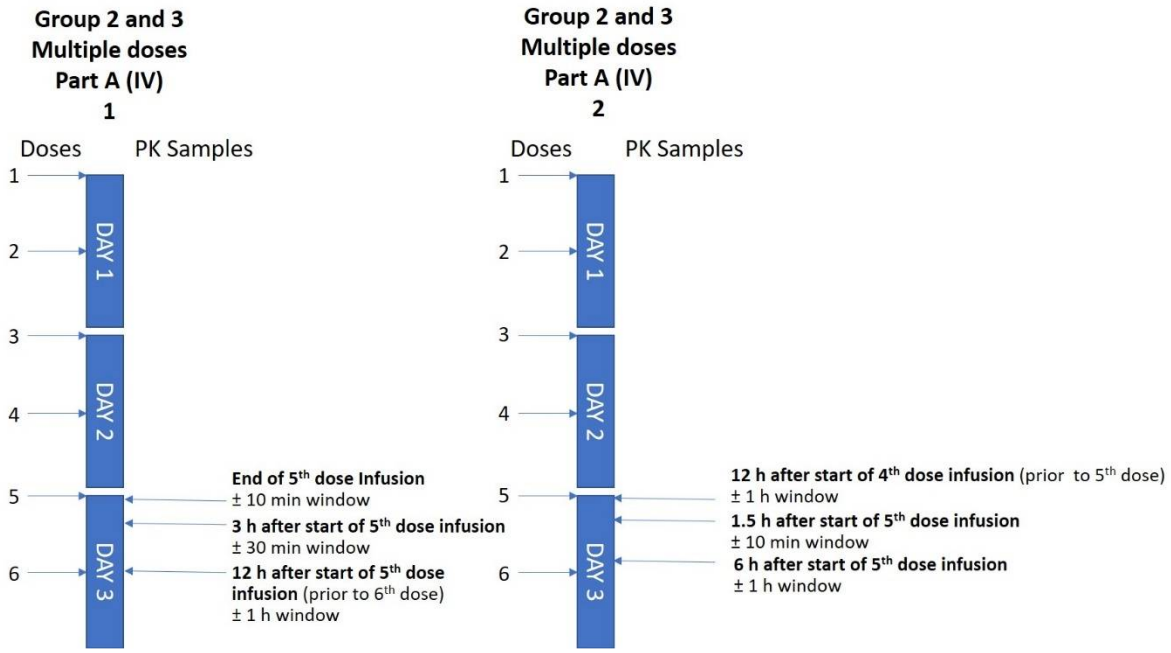
Figure 2, Figure 3, and Figure 4 provide the allowed windows for collection of blood samples.

Figure 2 Pharmacokinetic Sampling Schemes for Subjects Who Receive Single-dose Tedizolid Phosphate IV



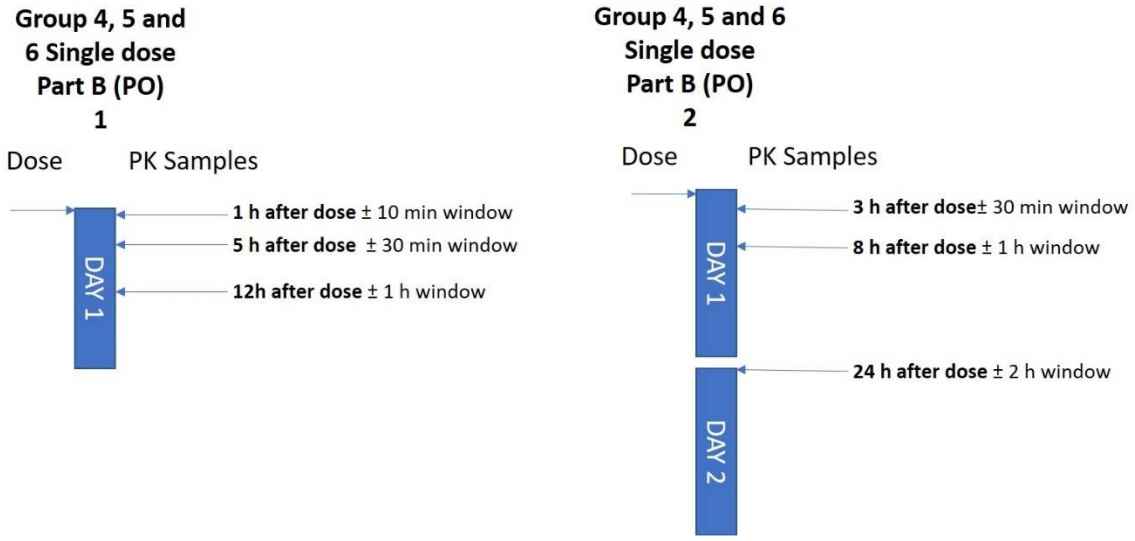
h=hour; IV=intravenous; min=minute(s); PK=pharmacokinetics

Figure 3 Pharmacokinetic Sampling Schemes for Subjects Who Receive Multiple-dose Tedizolid Phosphate



h=hour; IV=intravenous; min=minute(s); PK=pharmacokinetics

Figure 4 Pharmacokinetic Sampling Schemes for Subjects Who Receive Single-dose Tedizolid Phosphate Oral Suspension



h=hour; min=minutes; PK=pharmacokinetics; PO=oral

Note: PK samples will not be collected from subjects receiving oral suspension who vomit during and/or within 90 minutes after administration of a dose.

Exact time points of blood draws may be modified based on interim PK assessment (from this study).

Per individual, the trial-related blood loss (including any losses in the maneuver) will not exceed 3% of the total blood volume and will not exceed 1% at any single time (see Section 12.2). The total volume of blood is estimated at 80 to 90 mL/kg body weight; 3% is 2.4 mL blood per kg body weight.

7.1.3.2.3 Blood Collection for Plasma Levels of Tedizolid Phosphate and Tedizolid

Sample collection, storage and shipment instructions for plasma samples to evaluate the PK of tedizolid phosphate and its active metabolite, tedizolid, will be provided in the Laboratory Manual. Results of analysis will be reported separately.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen (eg, stop midway through an IV infusion) should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

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 Critical Equipment

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

Critical Equipment for this trial includes:

- Drug storage thermometer (which should have high/low recording)
- Local laboratory analytical instruments
- Sphygmomanometer
- Infusion pump

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 Visit

Within 4 days (inclusive, Day -3 to Day 1) prior to treatment allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Age eligibility will be assessed at the Screening Visit. Screening procedures may be repeated after consultation with the Sponsor. If a subject is rescreened, screening procedures should be repeated, unless they fall within the window specified. A subject may be rescreened only 1 time; age eligibility will be determined at rescreening.

7.1.5.2 Treatment Period Visits

Details of allocation to treatment (IV or oral) and PK sampling scheme are provided in Section 5.3. Details about the PK sampling schemes are provided in Section 7.1.3.2.2.

Details of blood sampling, processing, handling, and processing procedures will be provided in the Laboratory Manual.

7.1.5.3 Discontinued Subjects Continuing to be Monitored in the Trial

Subjects who discontinue treatment (including subjects who discontinue from study drug partway through an infusion) should have all safety assessments (including clinical safety labs, vital signs, physical examination, and collection of adverse events and medical history) completed as per Section 6.0, but do not need to have PK sampling performed. This is also true of subjects who “spit up” the oral dose.

Subjects who discontinue from the study prior to receiving a dose of treatment (eg, due to removal of consent by the parent or LAR, or due to an emergent condition or circumstance which, in the opinion of the investigator or sponsor, places the subject at unnecessary risk through continued participation, or does not allow adherence to the protocol) do not need to conduct further visits or assessments.

7.1.5.4 Post-Trial

The Post-treatment Follow-up Contact will be a follow-up assessment performed by telephone contact at least 14 days after administration of trial drug to determine if any adverse events have occurred since the previous visit.

The Follow-up Contact should be conducted in person if there are ongoing adverse events or clinically important laboratory abnormalities that require follow-up.

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 participant's legally authorized representative provides documented informed 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 14 days following cessation of treatment, 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 7.2.2.1. 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 is any dose higher than 1.25 times the protocol-specified dose of tedizolid phosphate. This threshold was selected conservatively, as on 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).

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 Immediate Reporting of Adverse Events to the Sponsor

7.2.2.1 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 5 for additional details regarding each of the above criteria.

For the time period beginning after documented informed consent is provided 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 14 days following cessation of treatment, 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.

7.2.2.2 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 documented informed consent is provided 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 14 days following cessation of treatment, 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 *C. difficile* infection such as toxic megacolon or pseudomembranous colitis.
3. Significant hematologic adverse events, defined as a clinically meaningful change in hemoglobin, platelet count, or absolute neutrophil count where one of these hematologic parameters reaches the following cutoff values by age (Table 4). 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 4 Cutoff Values for Hematological Events of Clinical Interest by Age

Laboratory Test by Age Group	Cutoff Value
Hemoglobin	
57 days to <13 y	<9.5 g/dL
36-56 days	<8.5 g/dL
22-35 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
2-7 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.

7.2.3 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 5. The investigator's assessment of causality is required for each adverse event. Refer to Table 5 for instructions in evaluating adverse events.

Table 5 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.)	

7.2.4 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.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the statistical analysis plan (SAP) (Section 8.2).

8.1.1 Statistical Methods

8.1.1.1 Safety

Summary statistics and plots will be generated for the change from baseline values at the interim analysis and the end of study, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log-scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

8.1.1.2 Pharmacokinetics

IV Administration (Group 1 Cohorts 1 and 2, Group 2, and Group 3)

A non-model based geometric mean of the AUC and C_{max} of tedizolid phosphate and its active metabolite, tedizolid, after administration (5^{th} dose or first dose on Day 3 for multiple-dose groups) will be calculated for each PK sampling scheme by age and dose (if dose adjusted at interim analysis) group. A ratio of non-model-based geometric mean between two PK sampling schemes will also be calculated by age group. If the ratio is greater than 2.0 or less than 0.5 for an age group, the naïve-pooled approach will be used to summarize the PK. In this approach, only one value for each PK parameter will be estimated for each age group, as specified in Section 7.1.3.2.1. If the ratio of non-model based geometric mean between two PK sampling schemes is within 0.5 and 2.0 for an age group, individual PK parameter values will be estimated. And an analysis of variance (ANOVA) model including factor for Group/Cohort will be used to analyze log transformed PK parameter values of tedizolid phosphate and tedizolid. Point estimates and two-sided 95% confidence intervals will be constructed for the geometric mean (GM) in pediatric subjects by Group/Cohort of AUC and C_{max} of tedizolid phosphate and tedizolid.

Oral Administration (Groups 4, 5 and 6)

The AUC of tedizolid phosphate and tedizolid, administered as oral suspension will be calculated using naïve-pooled approach as specified in Section 7.1.3.2.1. Only one value for AUC will be estimated for each age group.

The bioavailability will be estimated by dividing the naïve-pooled AUC from oral administrated subjects by the estimated AUC from IV administrated subjects, for each age

group. If the ratio of non-model based GM between two PK sampling schemes is between 0.5 and 2.0, then GM AUC estimate from ANOVA model will be used as the estimated AUC from IV administrated subjects. Otherwise, the naïve-pooled AUC estimate from each age group will be used. An average bioavailability will also be reported across age groups.

For IV administrated subjects with available individual PK parameter estimates, individual values will be listed for each PK parameter by age group, dose and PK sampling scheme, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 x sqrt[exp(s^2) - 1], where s^2 is the observed variance on the natural log-scale).

The effects of body weight and renal function on the PK parameter values may be graphically analyzed if appropriate. These data may be used in a population PK analysis.

8.1.1.3 Power

See Section 8.2.7.

8.2 Statistical Analysis Plan

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Pharmacology Department of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

8.2.1 Hypotheses

This is a descriptive, non-comparative study and no hypothesis testing is planned.

8.2.2 Analysis Endpoints

For all analyses, baseline is defined as the most recent measurement prior to the first administration of trial drug, unless otherwise specified.

Primary Endpoints

Pharmacokinetics: The pharmacokinetic variables for tedizolid phosphate and tedizolid ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, apparent terminal $t_{½}$,) are of interest.

Secondary Endpoints:

Safety: safety endpoints will include all types of adverse experiences, in addition to laboratory safety tests, and vital signs.

Exploratory Endpoints

Pharmacokinetics: bioavailability of tedizolid following administration of tedizolid phosphate oral suspension (Part B, Groups 4, 5 and 6).

The PK parameters are defined as follows:

$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to time of last quantifiable drug concentration
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve from time 0 extrapolated to infinity
CL or CL/F	Total body clearance or apparent total body clearance
Vd or Vd/F	Volume of distribution or apparent volume of distribution
C_{max}	Maximum concentration
T_{max}	Time to reach C_{max}
$t_{½}$	(*Apparent terminal*) Half-life
%BA	Percent bioavailability (oral only) calculated as (individual $AUC_{0\text{-inf}}$ PO * dose IV) / (mean $AUC_{0\text{-inf}}$ IV * dose PO) (for similar collection scheme), and overall for mean across both collection schemes, within and across all age groups

8.2.3 Approaches to Analyses

The following populations are defined for the analysis and reporting of data. All subjects will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Subjects as Treated (ASaT) - All subjects who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP) – The set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have valid samples collected for at least 2 of the assigned 3 time points will be included in the primary analysis dataset. This population will be used for the PK analyses.

8.2.4 Statistical Methods

8.2.4.1 Analysis Overview

All references within this data analysis section to the log transformation or log function pertain to the natural log. If log transformation is used, the confidence intervals for the means (mean differences) will be constructed on the natural log-scale and will reference the t-distribution. Exponentiating the least-squares means (mean differences) and lower and upper limits of these confidence intervals will yield estimates for the population geometric means

(population geometric mean ratios) and confidence intervals about the geometric means (geometric mean ratios) on the original scale.

Data will be examined for departures from the assumptions of the statistical model(s) as appropriate; eg, heteroscedasticity, non-normality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the models(s) is observed, or suitable data transformations may be applied.

8.2.4.2 Safety

Summary statistics and plots will be generated for the change from baseline values at the interim analysis and the end of study, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log-scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

8.2.4.3 Pharmacokinetics

Concentrations of tedizolid phosphate and tedizolid will be imputed as zero at time zero, where no samples were collected. Any missing postdose plasma concentrations will be treated as missing. Values below the limit of quantification (BLOQ) will be assigned a value of zero. For summary statistics of plasma concentration versus time data, at least half of the values at that timepoint must be >0 in order to report a value at that timepoint. At least 2 quantifiable postdose values are required for calculation of individual pharmacokinetics. AUC will be calculated using linear up/log down trapezoidal rule.

IV Administration (Group 1 [Cohort 1 and 2 Combined], Group 2, and 3)

A non-model-based GM of the AUC and C_{max} of tedizolid phosphate and its active metabolite, tedizolid after administration (5^{th} dose or first dose on Day 3 for multiple-dose groups) will be calculated for each PK sampling scheme by age and dose (if dose adjusted at interim analysis) group. A ratio of non-model based GM between two PK sampling schemes will also be calculated by age group. If the ratio is greater than 2.0 or less than 0.5 for an age group, the naïve-pooled approach will be used to summarize the PK. In this approach, only one value for each PK parameter will be estimated for each age group, as specified in Section 7.1.3.2.1. If the ratio of non-model based GM between two PK sampling schemes is within 0.5 and 2.0 for an age group, individual PK parameter values will be estimated. An ANOVA model including factor for Group/Cohort will be used to analyze log transformed PK parameter values of tedizolid phosphate and tedizolid. Point estimates and two-sided 95% confidence intervals will be constructed for the GM in pediatric subjects, by age group, for AUC and C_{max} of tedizolid phosphate and tedizolid.

Oral Administration (Groups 4, 5, and 6)

The AUC of tedizolid phosphate and tedizolid, administered as oral suspension will be calculated using naïve-pooled approach as specified in Section 7.1.3.2.1. Only one value for AUC will be estimated for each age group.

The bioavailability will be estimated by dividing the naïve-pooled AUC from oral administrated subjects by the estimated AUC from IV administrated subjects, for each age

group. If the ratio of non-model-based GM between two PK sampling schemes is between 0.5 and 2.0, then GM AUC estimate from ANOVA model will be used as the estimated AUC from IV administrated subjects. Otherwise, the naïve-pooled AUC estimate from each age group will be used. An average bioavailability will also be reported across age groups.

For IV administrated subjects with available individual PK parameter estimates, individual values will be listed for each PK parameter by age group, dose and PK sampling scheme, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 × sqrt[exp(s^2) - 1], where s^2 is the observed variance on the natural log-scale).

The effects of body weight and renal function on the PK parameter values may be graphically analyzed if appropriate. These data may be used in a population PK analysis.

8.2.5 Multiplicity

Since there are no prespecified hypotheses, no adjustments for multiplicity will be made.

8.2.6 Interim Analysis for Potential Dose Adjustment

The initial dose chosen at the time of the Initial Protocol has been modified to 3 mg/kg in Amendment 01, prior to enrollment of the first subject (see Section 4.2). Interim analyses are planned to evaluate the PK (eg, $AUC_{0-\infty}$) and safety profile and make dose adjustment, if deemed appropriate. Interim analyses will be conducted after PK data are available as follows:

1. The first 5 subjects from Group 1 (Cohort 1 and 2 combined), and
2. The first 6 subjects from Group 2, and
3. The first 6 subjects in Group 3.

Non-model-based summary statistics (including N, arithmetic mean, standard deviation, arithmetic percent CV, median, minimum, maximum, geometric mean, and geometric percent CV) of $AUC_{0-\infty}$ will be provided for each age group.

8.2.7 Sample Size and Power Calculations

Pharmacokinetics:

It is assumed that the variabilities of AUC and volume of distribution [Vd] of pediatric subjects are the same as those of adults as observed in pooled historical adult subjects from Studies MK-1986-008 (TR701-107) and MK-1986-031 (TR701-123).

Assuming the between-subject standard deviations of log(AUC) are 0.27 and 0.32 for tedizolid phosphate and tedizolid, respectively, with 10 completers in Group 1 (Cohort 1 and Cohort 2 combined), there are 99% and 97% probabilities that the 95% CI of GM is within 60% and 140% of the GM estimate; with 6 completers in Group 2 Cohort 1, there are 78% and 58% probabilities that the 95% CI of GM is within 60% and 140% of the GM estimate.

Assuming the between-subject standard deviations of log(Vd) are 0.28 and 0.29 for tedizolid phosphate and tedizolid, respectively, with 10 completers in Group 1 (Cohort 1 and Cohort 2 combined), there are 99% and 99% probabilities that the 95% CI of GM is within 60% and 140% of the GM estimate; with 6 completers in Group 2 Cohort 1, there are 74% and 70% probabilities that the 95% CI of GM is within 60% and 140% of the GM estimate.

Power calculations are not provided for subjects who receive multiple doses of tedizolid phosphate; the sample size was based on pragmatic considerations.

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 Table 6.

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 trial drug is tedizolid phosphate, also known as SIVEXTRO®.

Intravenous Form

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

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

Oral Suspension Form

Tedizolid Phosphate Powder for oral suspension is white to off-white powder for constitution into suspension for oral administration. The product is supplied in clear glass bottles, and includes the following inactive ingredients: potassium sorbate, silicon dioxide, succinic acid, sucrose, and xanthan gum. Additional information is provided in the Pharmacy Manual.

Table 6 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Tedizolid phosphate 200 mg	Lyophilized Powder for injection	Provided centrally by the Sponsor
Tedizolid phosphate (20 mg/mL)	Powder for Oral Suspension	Provided centrally by the Sponsor

All supplies indicated in Table 6 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 6 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.

No kitting is required.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

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's legally acceptable representative 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 Conference on Harmonization 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

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her

electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

[1] Tognetti L, Martinelli C, Berti S, Hercogova J, Lotti T, Leoncini F, et al. Bacterial skin and soft tissue infections: review of the epidemiology, microbiology, aetiopathogenesis and treatment. Journal of the European Academy of Dermatology and Venereology 2012:no.

[2] Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, Rybak MJ, Talan DA, Chambers HF. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children. Clin Infect Dis 2011:52 (1 February)

[3] Cosgrove SE. The Relationship between Antimicrobial Resistance and Patient Outcomes: Mortality, Length of Hospital Stay, and Health Care Costs. Clin Infec Dis, 2006; 42:S82–9

[4] Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, Briggs JP, Sexton DJ, Kaye KS. Adverse Clinical and Economic Outcomes Attributable to Methicillin Resistance among Patients with Staphylococcus aureus Surgical Site Infection. Clin Infect Dis 2003; 36:592–8

[5] Elliott DJ, Zaoutis TE, Troxel AB, Loh A, Keren R. Empiric Antimicrobial Therapy for Pediatric Skin and Soft-Tissue Infections in the Era of Methicillin-Resistant Staphylococcus aureus. PEDIATRICS Volume 123, Number 6, June 2009

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/Tissue Volumes Drawn/Collected 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 many centers suggesting a 0.5-mL draw for most standard clinical tests in neonates (blood culture, hematology with differential, and clinical chemistry panels). With this recognition in mind, expected blood volumes for the youngest age group (neonates) are calculated below for subjects who receive single-dose tedizolid phosphate (all subjects except those who receive multiple-dose tedizolid phosphate in Group 2 and 3):

Trial Visit/Cycle/etc:	Screening Visit 1	Allocation & Treatment Visit 2	Day 2-3 Visit Visit 3	Total
Hematology	0.5 mL		0.5 mL	1.0 mL
Serum/Plasma Chemistry	0.5 mL		0.5 mL	1.0 mL
PK samples		0.3 mL (3 × 0.1 mL)		0.3 mL
Expected Total (mL)	1.0 mL	0.3 mL	1.0 mL	2.3 mL

For subjects who receive multiple doses in Groups 2 and 3, 2.3 mL of total blood will be withdrawn during the study:

Trial Visit/Cycle/etc:	Screening Visit 1	Allocation & Treatment Visit 2	Day 2-3 Visit Visit 3	Total
Hematology	0.5 mL		0.5 mL	1.0 mL
Serum/Plasma Chemistry	0.5 mL		0.5 mL	1.0 mL
PK samples*			0.3 mL (3 × 0.1 mL)	0.3 mL
Expected Total (mL)	1.0 mL		1.3 mL	2.3 mL

*For subjects assigned to PK sampling Scheme 1, 2 samples are collected at each of Visits 2 and 3. For subjects assigned to PK sampling Scheme 2, 1 sample is collected at Visit 2 and 3 samples are collected at Visit 3 (see Section 7.1.3.2.2).

The total volume drawn is within an allowable amount of 3% of total blood volume (2.4 mL blood per kg of body weight), even for the smallest neonates allowed in this study (1.0 kg).

While larger volumes may be collected per local laboratory policies for laboratory testing in older children, no more than 3% of the total blood volume should be drawn during the course of this study.

12.3 Examples of Prohibited Concomitant Medications With Potential Serotonergic Activity

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

Receipt of the following medications is prohibited in the 14 days prior to randomization through the Post-treatment Visit.

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	

12.4 Abbreviations

Abbreviations and Definitions of Terms

The following terms may be used interchangeably within the document:

- Subject and participant
- Trial and study

Abbreviation or Term	Explanation
%BA	Percent bioavailability
ABSSSI	Acute bacterial skin and skin structure infections
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ASaT (population)	All subjects as treated
AST	Aspartate aminotransferase
AUC	Area under the time-concentration curve
BCRP	Breast cancer resistance protein
BP	Blood pressure
CA-MRSA	Community-acquired methicillin-resistant *Staphylococcus aureus*
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Total body clearance (of study treatment)
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CSR	Clinical study report
cSSTI	Complicated skin and soft tissue infection
EDC	Electronic data capture
ECG	Electrocardiogram
ECI	Event of clinical interest
e-CRF	Electronic case report form
EMA	European Medicines Agency
EOT	End of therapy
EU	European Union
F	Bioavailability
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Modernization Act
FDAMA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
GM	Geometric mean
GMP	Good Manufacturing Practice
HA-MRSA	Hospital-acquired methicillin-resistant *Staphylococcus aureus*
HR	Heart rate
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	International Ethics Committee
IRT	Interactive response technology
IV	Intravenous

Abbreviation or Term	Explanation
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MK-1986	Tedizolid phosphate (SIVEXTRO®)
MRSA	Methicillin-resistant *Staphylococcus aureus*
PK	Pharmacokinetic(s)
PP	Per-protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedures
SSRI	Selective serotonin reuptake inhibitor
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time of maximum serum concentration
TR701	Tedizolid
TR701 FA	Tedizolid phosphate
TZD	Tedizolid phosphate
US	United States
Vd	Volume of distribution
WBC	White blood cell

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	