

Official Protocol Title:	A Phase 1, Single-Administration Pharmacokinetic and Safety Study of Oral and IV Tedizolid Phosphate in Hospitalized Subjects 2 to <12 Years Old
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Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase 1, Single-Administration Pharmacokinetic and Safety Study of Oral and IV Tedizolid Phosphate in Hospitalized Subjects 2 to <12 Years Old

IND NUMBER: [106,307 (IV) *and* 125,076 (Oral Suspension)]

EudraCT NUMBER: 2015-004595-29

SUMMARY OF CHANGES: TR701-120 Amendment 4

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section	Change	Rationale
1.0 Synopsis Methodology; Investigational product, dosage and mode of administration 6.1 Overall Study Design	Updated dose for 6 to <12 years from 5 mg/kg to 4mg/kg, dose for 2 to <6 years from 5 mg/kg to 6 mg/kg based on the data from interim safety and pharmacokinetic analyses; updated with alternative enrollment sequences for both older and younger age groups.	The dose level for the two age groups was adjusted based on the results of the first interim analysis of the safety and pharmacokinetic data. The new dose levels are expected to provide a closer match to the adult pharmacokinetic parameters. The order of dosing groups was also adjusted to allow the flexibility to enroll the second IV cohorts for each age group, wholly or in part, prior to initiation of the oral groups, in case there is a delay in the availability of the tedizolid phosphate oral suspension. This flexibility will minimize the duration of the trial and allow continued enrollment in the study since the initiation of other clinical trials is dependent on the results of MK-1986-013, and does not impact the assessment of appropriate doses for subsequent age.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section	Change	Rationale
Title Page	Changed the sponsor address	Corrected business address (business address of Cubist, rather than Merck & Co.).
1.0 Synopsis Name of Sponsor/Company; Investigators	Updated the Sponsor name from “a wholly-owned subsidiary of Merck” to “a wholly-owned subsidiary of Merck Sharp & Dohme Corp”; remove row of Investigators.	Corrected Sponsor name; removed row of Investigators as this information is not necessary for the synopsis of the protocol.
3.0 List of Abbreviations and Definition of Terms	Added PfOS, Powder for Oral Suspension to the list.	Updated the list.

Section	Change	Rationale
4.0 Introduction	Separated TR701-120 (MK-1986-013) from planned studies to ongoing studies in Table 2.	Reflected current studies' status.
6.1 Overall Study Design	Added rescreening language.	Clarified if a subject does not meet certain entry criteria, rescreen is allowed.
8.2 Concomitant Medications	Added reference number of monoamine oxidase inhibitors or serotonergic agents.	Made it easier for reference.
9.2.1 Intravenous Tedizolid Phosphate	Removed "Calculations of" from "Calculations of dose allowable volumes, and infusion rate required are provided in the Pharmacy Manual".	Site is not required to calculate the dose but should look for the dose provided in the pharmacy manual.
9.2.2 Oral Tedizolid Phosphate	Removed "Calculations of" from "Calculations of volume required is provided in the Pharmacy Manual."	Site is not required to calculate the volume but should look for the volume provided in the pharmacy manual.
10.2.2 Definition of an Overdose for this Protocol and Reporting an Overdose to the Sponsor	Clarified the nominal dose used to report an overdose for this trial is based on age group and body weight.	Clarified the nominal dose to ensure accurate reporting of an overdose.
12.2 Samples	Updated "Part V" to "Part B" in Table 5 Pharmacokinetic sampling scheme; added footnote stating if a subject vomits during and/or after oral dose administration within 1.5 hours, PK samples will not be collected. However, vomiting must be recorded as AE.	Corrected the typing error; subjects who vomit during oral dosing will not get the full dose of the study drug. Therefore, PK sample should not be collected. However, vomiting itself is considered as an adverse event, and should be reported as such.

Section	Change	Rationale
19.0 Appendix D Schedule of Study Assessments	Updated footnote (b) to allow ECGs collected within the 30 days prior to screening to be used to satisfy the entry criterion; updated footnote (c) removed oral from the measurement of temperature but added the consistent method should be used to obtain body temperature; removed “supine” from measurement of resting BP but added that it should be measured in the same position each time.; updated footnote (f) from “HDYF inquiry performed at each vital signs measurement” to “HDYF inquiry performed at vital signs measurement, once daily”; added footnote (i) to clarify that safety labs collected as part of standard care can be used for screening if they are within the 7 days prior to dosing.	Clarified prior ECG and safety laboratory collected prior to the study can be used to satisfy entry criteria if meets the required window; multiple methods of measuring temperature in children are standard and permissible; as long as resting BP is measured in a consistent fashion, it will allow for monitoring of changes.; HDYF is only intended to be asked once per day, rather than at every blood pressure measurement; allowance of prior lab values as long as they are within 7 days prior to receipt of study drug minimizes blood sampling and stress/distress to the child.
19.0 Appendix E Examples of Prohibited Concomitant Medications	Added examples of prohibited medications related to exclusion criterion #11	Provided reference.
Global	Minor edits.	

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for tedizolid phosphate. I have read the TR701-120 protocol and agree to conduct the study as outlined. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to this protocol. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Phase 1, Single-Administration Pharmacokinetic and Safety Study of Oral and IV Tedizolid Phosphate in Hospitalized Subjects 2 to <12 Years Old

Printed Name of Investigator

Signature of Investigator

Date

1.0 SYNOPSIS

Name of Sponsor/Company: Cubist Pharmaceuticals, LLC (Cubist), a wholly-owned subsidiary of Merck Sharp & Dohme Corp.	
Name of Investigational Product: Tedizolid Phosphate	
Name of Active Ingredient: tedizolid phosphate	
Title of Study: Phase 1, Single-Administration Pharmacokinetic and Safety Study of Oral and IV Tedizolid Phosphate in Hospitalized Subjects 2 to <12	
Study center(s): Approximately 20	
Study period (years): Estimated date first subject enrolled: May 2016 Estimated date last subject completed: April 2018	Phase of development: 1
Objectives: Part A (Intravenous [IV] Study Drug Administration) <u>Primary objective:</u> To describe the single-administration pharmacokinetics (PK) of IV tedizolid phosphate (TZD) and its active metabolite, tedizolid, in subjects ages 6 to <12 years (Group 1) and 2 to <6 years (Group 2). <u>Secondary objective:</u> To evaluate the safety and tolerability of IV TZD administration in subjects ages 6 to <12 years (Group 1) and 2 to <6 years (Group 2). Part B (Oral Study Drug Administration) <u>Primary objective:</u> To describe the bioavailability of tedizolid following oral TZD administration to subjects ages 6 to <12 years (Group 3) and 2 to <6 years (Group 4). <u>Secondary objective:</u> <ul style="list-style-type: none">To evaluate the safety and tolerability of oral TZD administration in subjects ages 6 to <12 years (Group 3) and 2 to <6 years (Group 4).To evaluate the palatability of oral TZD suspension in subjects ages 6 to <12 years (Group 3) and 2 to <6 years (Group 4).	
Study Rationale: Safety and PK results will determine the appropriate dose for a subsequent safety and efficacy study in children from 3 months to <12 years, and for PK studies in younger children, i.e., preterm and full-term neonates, and infants/toddlers.	

Methodology: This is an open-label, multicenter, 2-part, single-administration study to assess the PK of TZD and its active metabolite, tedizolid, and the safety of TZD following administration of a single IV (Part A) or oral (Part B) administration to hospitalized subjects ages 6 to <12 years (Groups 1 and 3, respectively), and 2 to <6 years (Groups 2 and 4, respectively). Subjects receiving prophylaxis for or being treated for a confirmed or suspected infection with Gram-positive bacteria will be enrolled. The IV groups will be split into 2 cohorts of 5 subjects each. Prior to this amendment, 5 subjects ages 6 to <12 from Cohort 1 of Group 1 received the study drug at dose of 5 mg/kg of total body weight. The table below summarizes the parts (administration route), groups (age), and cohorts (dose) of the amended study.

Part A – IV administration	Dose
Group 1: 6 to <12 years (N=10)	Cohort 1: 5 mg/kg (completed) Cohort 2: 4 mg/kg
Group 2: 2 to <6 years (N=10)	Cohort 1: 6 mg/kg Cohort 2: 6 mg/kg or modified
Part B – Oral administration	
Group 3: 6 to <12 years (N=6)	4 mg/kg
Group 4: 2 to <6 years (N=6)	6 mg/kg or modified

TZD will be administered to subjects any time after antimicrobial administration with a non-study antibiotic has been initiated.

Progression to younger ages will be conducted as follows:

The first group enrolled was Group 1 Cohort 1; following enrollment of all 5 patients in this cohort, a preliminary analysis took place to review the pharmacokinetic and safety data to confirm or adjust the dose for the remaining subjects in this age range (Group 1 Cohort 2 and Group 3). Analysis of the safety data indicate that the 5 mg/kg dose is well tolerated. Pharmacokinetic analyses indicated the appropriate dose level for subjects 6 to < 12 years should be adjusted downward to 4 mg/kg, and for subjects 2 to <6 years old adjusted upward to 6 mg/kg, to better match to adult pharmacokinetic parameters and increase the likelihood of target attainment in later efficacy and safety studies. The modified dose level was communicated to sites via a memo and a revised Pharmacy Manual.

The younger age range will follow a similar sequence, with a preliminary analysis of PK and safety after the first cohort of Group 2 receiving 6 mg/kg IV has been enrolled, in order to confirm or adjust the dose for the remaining subjects in this age range (Group 2 Cohort 2 and Group 4).

In order to expedite the initiation of later studies that depend on oral and IV PK data, further enrollment in the 6 to <12 years age range was planned to initiate with Group 3 (oral), to evaluate bioavailability, prior to enrolling the remainder of the IV Group 1 Cohort 2. A similar sequence of enrollment (IV Group 2 Cohort 1, Oral Group 4, and IV Group 2 Cohort 2) is planned for enrollment of the lower age group.

However, it is not necessary to evaluate bioavailability prior to selecting an appropriate dose and proceeding with dosing in IV Group 1 Cohort 2 or Group 2 Cohort 2. Under

Amendment 4, the order of dosing for either age group is now flexible and can be altered as follows. If the powder for oral suspension is not available at the time of planned oral group enrollment, enrollment of the second IV cohort may be initiated prior to enrollment of the oral cohort. In this case, enrollment of the oral dosing group will be initiated as soon as the oral suspension is available, whether the enrollment of the second IV cohort is completed or not. If the oral group is started before the second IV cohort is completed, enrollment in the second IV cohort will be paused and second IV cohort will only be completed once the full oral group is enrolled. A bioavailability assessment will also be performed following completion of Group 3; available PK data from all prior cohorts in the study will be used to inform the dose selection of Group 4.

In addition to safety (clinical laboratory evaluations; physical, examinations; adverse events), palatability will be assessed in oral TZD suspension in subjects ages 6 to <12 years (Group 3) and 2 to <6 years (Group 4). Subjects will receive study drug on Day 1, with study visits on Day 2 and Day 8. The Day 8 Visit may be a telephone contact.

Number of subjects (planned): At least 32 subjects will be enrolled in this study to ensure at least 28 subjects with complete PK profiles.

Part A: At least 20 subjects will be enrolled to receive IV TZD (10 subjects in Groups 1 and 10 subjects in Group 2 [5 subjects in each of 2 cohorts]).

Part B: At least 12 subjects will be enrolled to receive oral TZD (6 subjects in Group 3 and 6 subjects in Group 4).

Criteria for Inclusion:

1. Aged 2 to <12 years at the time of consent
2. Receiving prophylaxis for or with a confirmed or suspected infection with Gram-positive bacteria and receiving concurrent antibiotic treatment with Gram-positive antibacterial activity
3. Weight >5th percentile and <95th percentile based on age (http://www.cdc.gov/growthcharts/clinical_charts.htm)
4. Stable condition as determined from medical history, physical examination, electrocardiogram (minimally 5-lead), vital signs, and clinical laboratory evaluations
5. No clinically significant ECG abnormalities in the judgment of the Investigator
6. Serum creatinine within 1.5 × upper limit of reference range based on age
7. Females must be pre-menarchal, abstinent, or practicing an effective method of birth control
8. Negative blood or urine beta-human chorionic gonadotropin pregnancy test (if urine test is used, it must be high sensitivity [i.e., able to detect 10 mIU/mL β-hCG]) at the Screening Visit (post-menarchal females only)
9. Subjects and parents must be willing to adhere to the prohibitions and restrictions specified in this protocol
10. Parents or subjects' legally authorized representative (LAR) able to give informed consent and willing and able to comply with all required study procedures. Assent is also required of children capable of understanding the nature of the study (typically ≥7 years old)

Criteria for Exclusion:

1. History of seizures, other than febrile seizures, clinically significant cardiac arrhythmia, cystic fibrosis, 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. Use of rifampin within, 14 days prior to study drug administration
3. Use of ranitidine, cimetidine, and antacids for subjects in Part B (oral administration) from 24 hours prior to study drug administration and throughout the study
4. Recent (3 month) history or current infection with viral hepatitis or other significant hepatic disease
5. History of drug allergy or hypersensitivity to oxazolidinones
6. Pregnant or breast feeding
7. Significant blood loss ($\geq 5\%$ of total blood volume) within 60 days before the Screening Visit
8. 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
9. Treatment with investigational medicinal product within 30 days before the infusion/dose of study drug
10. 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.)
11. Use of monoamine oxidase inhibitors or serotonergic agents including tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin 5 hydroxytryptamine receptor agonists (triptans), meperidine, or buspirone within, 14 days prior to study, or planned use while on study

Investigational product, dosage and mode of administration:

Five subjects of Group 1 Cohort 1 received a single dose of 5 mg/kg dose prior to this amendment.

Under this amendment, subjects 6 to <12 years of age will receive a single 4 mg/kg dose TZD, and subjects 2 to <6 years of age will receive a 6 mg/kg dose (with possible adjustment based on data from preliminary analyses), as either an IV infusion (Tedizolid Phosphate for Injection, 200 mg/vial diluted into sterile saline for injection; infused at a rate to deliver the desired dose in 60 minutes [up to 200 mg]; Part A) or an oral suspension (Part B). See Pharmacy Manual for instructions, including allowable IV volumes.

Duration of study: Enrollment will be completed within approximately 2 years. The overall duration of the study will be up to 11 days from the Screening Visit through the last visit (Day 8), unless a subject is being monitored for an a serious adverse event (SAE). Subjects will be monitored for AEs through 7 days after study drug administration and SAEs will be followed until stabilization, resolution/death, or consent/assent is withdrawn.

Criteria for evaluation: Safety

Safety evaluations will include laboratory evaluations (hematology, serum chemistry, and urinalysis; see APPENDIX A. CLINICAL LABORATORY EVALUATIONS), pregnancy testing (for females of childbearing potential in Groups 1 and 3), vital signs, physical examinations, monitoring of AEs, recording of concomitant medications, and monitoring of venous tolerability (for subjects who receive IV drug).

PK

Plasma samples will be analyzed for concentrations of TZD and its active metabolite, tedizolid. Based on the individual plasma concentration-time data, using actual sampling times, PK parameters for tedizolid and TZD including the following will be determined:

- maximum observed drug concentration in plasma (C_{max})
- time to reach peak plasma concentration (t_{max})
- area under the plasma concentration-time curve (AUC)
- terminal elimination half-life ($t_{1/2}$)
- clearance after oral and IV administration (CL/F and CL, respectively)

Palatability: Palatability will be assessed using a hedonic scale (see APPENDIX B. PALATABILITY ASSESSMENT) and spontaneous verbal judgment.

Analysis Sets:

The Intent to Treat analysis set will consist of data from all enrolled subjects. Enrolled subjects include all subjects whose designee signs the Informed Consent Form.

The Safety analysis set will consist of data from subjects who receive any study drug.

The PK analysis set will consist of data from subjects who receive study drug and have at least 1 quantifiable post-administration concentration.

Statistical methods:

No formal statistical tests are planned. The planned sample size is not based on a power calculation; sample size is similar to other pediatric PK studies.

Study data will be presented using summary statistics by group (Groups 1-4). Continuous study data will be summarized with the number of subjects, mean standard deviation, median, minimum, and maximum. Categorical data will be summarized with the number and percentage in each category. Demographic information and baseline characteristics will be summarized by age group and dose cohort. For PK summaries, geometric means and coefficients of variation will be calculated, as appropriate.

PK analyses

Descriptive statistics will be presented for tedizolid and TZD plasma concentrations by group. Mean and individual plasma concentration-time profiles will be plotted in linear and semilogarithmic scales. All TZD and tedizolid PK parameters will be summarized by treatment using summary statistics.

Safety data

Safety data will be tabulated and summarized separately for each age group and dose cohort.

The number and percentage of subjects reporting treatment-emergent AEs (TEAEs) will be presented by System Organ Class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), by relationship to the study drug administration and by severity.

Hematology and chemistry laboratory data, and vital signs data will be summarized using summary statistics. Changes from the Screening Visit to Day 2 will also be summarized for laboratory and vital signs data. All safety data will be listed.

Palatability assessments of oral suspension will be analyzed using descriptive statistics.

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3.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1 Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ABSSSI	Acute bacterial skin and skin structure infections
AE	Adverse event
AUC	Area under the plasma concentration-time curve
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance after IV administration
CL/F	Clearance after oral administration
C _{max}	Maximum observed drug concentration in plasma
cSSTIs	Complicated skin and soft tissue infections
ECG	Electrocardiogram
e-CRF	Electronic case report form
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intent to treat
LAR	Legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
PDCO	EMA/Paediatric Committee
PfOS	Powder for Oral Suspension
PK	Pharmacokinetics
SAE	Serious adverse event
SOC	System organ class
t _{1/2}	Terminal elimination half-life
TEAE	Treatment-emergent adverse events
t _{max}	Time to reach peak plasma concentration
TZD	Tedizolid phosphate
WHO	World Health Organization

4.0 INTRODUCTION

Tedizolid phosphate (Sivextro™, TR-701 FA, MK-1986) is a novel oxazolidinone prodrug antibiotic that is rapidly converted in vivo by phosphatases to the microbiologically active moiety tedizolid

(TR-700). Tedizolid is a protein synthesis inhibitor that interacts with the 50S subunit of the bacterial ribosome. Tedizolid has bacteriostatic activity against Gram-positive bacteria including common skin pathogens *Staphylococcus aureus* (both methicillin-sensitive and –resistant strains) and *Streptococcus pyogenes*, less common species causing acute bacterial skin and skin structure infections (ABSSSI), *S. anginosus-milleri* group and *Enterococcus faecalis*, and other Gram-positive aerobes and anaerobes. New drug applications for tedizolid phosphate for the indication of ABSSSI were approved by the Food and Drug Administration (FDA) 20 June 2014. A Marketing Authorization Application was approved by the European Medicines Agency (EMA) on 23 March 2015.

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

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

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

The EMA/Paediatric Committee (PDCO) issued a Pediatric Investigation Plan Positive Opinion in October 2013 for the treatment of complicated skin and soft tissue infections (cSSTIs). The

proposed FDA Pediatric Study Plan was submitted with the new drug applications in October 2013, and reflects the outcome of the EMA/PDCO discussions and meetings with the FDA. These studies are described in [Table 2](#).

Table 2 Pediatric Studies

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

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

Results of Study TR701-111 established that exposure was similar in adults and adolescents and that tedizolid phosphate was well-tolerated with no clinically significant safety findings in 20 adolescent subjects. An initial adolescent population PK model was used to simulate concentrations for younger pediatric age groups using allometric scaling. These simulations support an estimated dose of 5 mg/kg tedizolid phosphate in the pediatric population.

The proposed study is a safety and PK study of single-administration oral or IV tedizolid phosphate in hospitalized subjects 2 to <12 years old receiving prophylaxis for or being treated for a confirmed or suspected infection with Gram-positive bacteria. Safety and PK results from this study will determine the appropriate dose for a subsequent safety and efficacy study in children 3 months to <12 years, and for PK studies in younger children (i.e., preterm and full-term neonates, and infants/toddlers).

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

5.0 TRIAL OBJECTIVES AND PURPOSE

5.1 Primary Objective

Part A (IV Study Drug Administration)

To describe the single-administration PK of IV tedizolid phosphate and its active metabolite, tedizolid, in subjects ages 6 to <12 years (Group 1) and 2 to <6 years (Group 2).

Part B (Oral Study Drug Administration)

To describe the bioavailability of tedizolid following oral tedizolid phosphate administration to subjects ages 6 to <12 years (Group 3) and 2 to <6 years (Group 4).

5.2 Secondary Objective

Part A (IV Study Drug Administration)

To evaluate the safety and tolerability of IV tedizolid phosphate administration in subjects ages 6 to <12 years (Group 1) and 2 to <6 years (Group 2).

Part B (Oral Study Drug Administration)

To evaluate the safety and tolerability of oral tedizolid phosphate administration in subjects ages 6 to <12 years (Group 3) and 2 to <6 years (Group 4).

To evaluate the palatability of oral tedizolid phosphate suspension in subjects ages 6 to <12 years (Group 3) and 2 to <6 years (Group 4).

6.0 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This is an open-label, multicenter, 2-part, single-administration study to assess the PK of tedizolid phosphate and its active metabolite, tedizolid, and the safety of tedizolid phosphate following administration of a single IV (Part A) or oral (Part B) administration to hospitalized subjects ages 6 to <12 years (Groups 1 and 3, respectively), and 2 to <6 years (Groups 2 and 4, respectively). Subjects receiving prophylaxis for or being treated for a confirmed or suspected infection with Gram-positive bacteria will be enrolled. The IV groups will be split into 2 cohorts of 5 subjects each. Prior to this amendment, 5 subjects ages 6 to <12 from Cohort 1 of Group 1 received the study drug at dose of 5 mg/kg of total body weight. [Table 3](#) summarizes the parts (administration route), groups (age), and cohorts (dose) of the amended study.

Table 3 Study TR701-120 Parts, Groups, and Cohorts

Part A – IV administration	Dose
Group 1: 6 to <12 years (N=10)	Cohort 1: 5 mg/kg (completed) Cohort 2: 4 mg/kg
Group 2: 2 to <6 years (N=10)	Cohort 1: 6mg/kg Cohort 2: 6 mg/kg or modified
Part B – Oral administration	
Group 3: 6 to <12 years (N=6)	4 mg/kg
Group 4: 2 to <6 years (N=6)	6 mg/kg or modified

Tedizolid phosphate will be administered to subjects any time after antimicrobial administration with a non-study antibiotic has been initiated.

Progression to younger ages will be conducted as follows:

The first group enrolled was Group 1 Cohort 1; following enrollment of all 5 patients in this cohort, a preliminary analysis took place to review the pharmacokinetic and safety data in order to confirm or adjust dose for the remaining subjects in this age range (Group 1 Cohort 2 and Group 3). Analysis of the safety data indicate that the 5 mg/kg dose is well tolerated. Pharmacokinetic analyses indicated the appropriate dose level for subjects 6 to < 12 years old should be adjusted downward to 4 mg/kg, and for subjects 2 to <6 years old adjusted upward to 6 mg/kg, to better match to adult pharmacokinetic parameters and increased the likelihood of target attainment in later efficacy and safety studies. The modified dose level was communicated to sites via a memo and a revised Pharmacy Manual.

The younger age range will follow a similar sequence, with a preliminary analysis of PK and safety after the first cohort of Group 2 receiving 6 mg/kg IV has been enrolled, in order to confirm or adjust the dose for the remaining subjects in this age range (Group 2 cohort 2 and Group 4).

In order to expedite the initiation of later studies that depend on oral and IV PK data, further enrollment in the 6 to <12 years age range was planned to initiate with Group 3 (oral), to evaluate bioavailability prior to enrolling the remainder of the IV Group 1 Cohort 2. A similar sequence of enrollment (IV Group 2 Cohort 1, Oral Group 4, and IV Group 2 Cohort 2) was planned for enrollment of the lower age group.

However, it is not necessary to evaluate bioavailability prior to selecting an appropriate dose and proceeding with dosing in IV Group 1 Cohort 2 or Group 2 Cohort 2. Under Amendment 4, the order of dosing for either age group is now flexible and can be altered as follow. If the powder for oral suspension is not available at the time of planned oral group enrollment, enrollment of the second IV cohort may be initiated prior to enrollment of the oral cohort. In this case, enrollment of the oral dosing group will be initiated as soon as the oral suspension is available whether the

enrollment of the second IV cohort is completed or not. If the oral group is started before the second IV cohort is completed, enrollment in the second IV cohort will be paused and the second IV cohort will only be completed once the full oral group is enrolled. A bioavailability assessment will also be performed following completion of Group 3; available PK data from all prior cohorts in the study will be used to inform the dose selection of Group 4.

In addition to safety (clinical laboratory evaluations; physical examinations; adverse events), palatability will be assessed in oral tedizolid phosphate suspension in subjects ages 6 to <12 years (Group 3) and 2 to <6 years (Group 4). Subjects will receive study drug on Day 1, with study visits on Day 2 and Day 8. The Day 8 Visit may be a telephone contact.

Study treatment may be discontinued at the subject's/LAR's request, in the case of unacceptable toxicity or pregnancy, or if the Investigator believes changing therapy would be in the best interest of the subject.

The overall duration of the study is expected to be approximately 24.5 months (24 months for enrollment, 11 days from the Screening Visit through last visit [Study Day 8]). Subject participation may be extended if a subject is being monitored for an SAE. Subjects will be monitored for AEs through 7 days after study drug administration and SAEs will be followed until stabilization, resolution/death, or consent/assent is withdrawn.

Rescreen is permitted two times if a subject initially does not meet eligibility but later does.

A scheme showing the study visit schedule is presented in [Figure 1](#), and enrollment progression in [Figure 2](#). APPENDIX D SCHEDULE OF STUDY ASSESSMENTS presents the detailed schedule of assessments.

Figure 1 Study Scheme for TR701-120

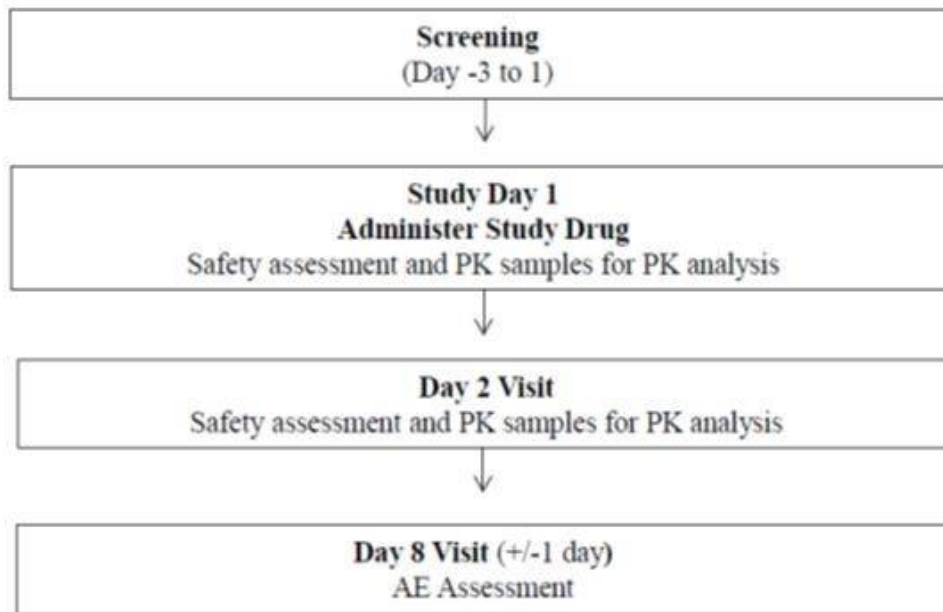
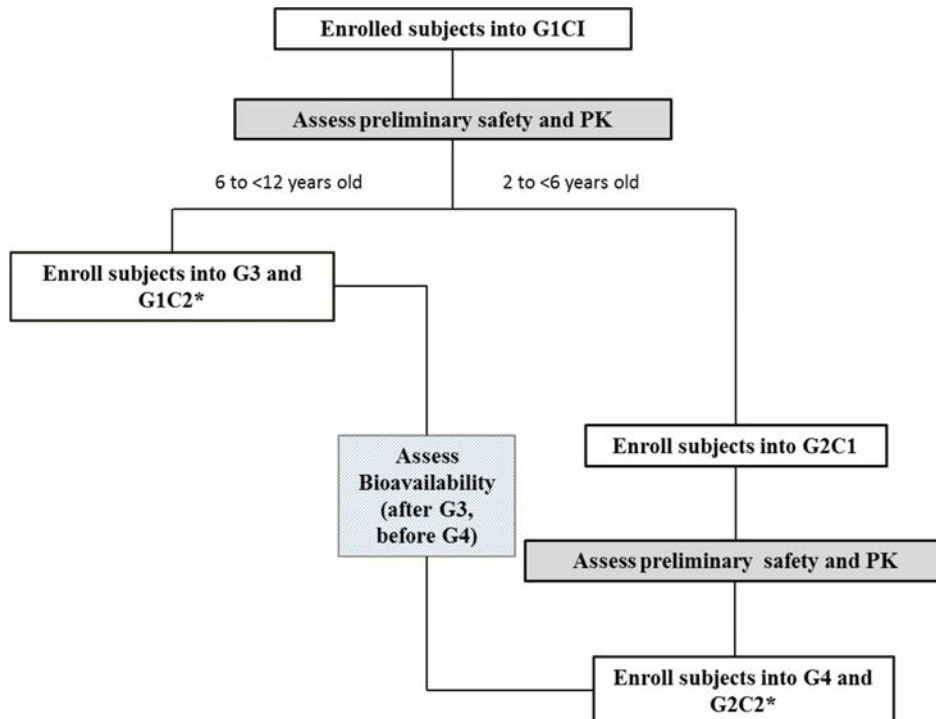


Figure 2 Study Progression for TR701-120: Oral and IV administration



*Oral suspension groups G3 and G4 will be prioritized over IV groups, G1C2 and G2C2, as soon as the Powder for Oral Suspension (PfOS) is available. If enrollment of G1C2 or G2C2 has not completed before PfOS availability (start of Oral enrollment); then G1C2 and/or G2C2 will resume enrollment after completion of the oral groups (G3 and G4).

Abbreviations: C=Cohort, G=Group, PK=pharmacokinetics

6.2 Number of Subjects

At least 32 subjects will be enrolled in this study to ensure at least 28 subjects with complete PK profiles.

Part A IV Administration: At least 20 (15 additional, as of amendment 3) subjects will be enrolled to receive IV tedizolid phosphate (10 subjects ages 6 to <12 years in Group 1, of which the first cohort of 5 subjects has been enrolled; and 10 subjects ages 2 to <6 years enrolled in Group 2 [5 subjects in each of 2 cohorts]; 9 completed in each Group).

Part B Oral Administration: At least 12 subjects will be enrolled to receive oral tedizolid phosphate (6 subjects ages 6 to <12 years enrolled in Group 3 and 6 subjects ages 2 to <6 years enrolled in Group 4; 5 completed in each Group).

6.3 Treatment Assignment

This study is an open-label study and thus no randomization to study treatment is required.

7.0 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Subject Inclusion Criteria

1. Aged 2 to <12 years at the time of consent
2. Receiving prophylaxis for or with a confirmed or suspected infection with Gram-positive bacteria and receiving concurrent antibiotic treatment with Gram-positive antibacterial activity
3. Weight >5th percentile and <95th percentile based on age (http://www.cdc.gov/growthcharts/clinical_charts.htm)
4. Stable condition as determined from medical history, physical examination, ECG (minimally 5-lead), vital signs, and clinical laboratory evaluations
5. No clinically significant ECG abnormalities in the judgment of the Investigator
6. Serum creatinine within $1.5 \times$ upper limit of reference range based on age
7. Females must be pre-menarchal, abstinent, or practicing an effective method of birth control
8. Negative blood or urine beta-human chorionic gonadotropin pregnancy test (if urine test is used, it must be high sensitivity [i.e., able to detect 10 mIU/mL β -hCG]) at the Screening Visit (post-menarchal females only)

9. Subjects and parents must be willing to adhere to the prohibitions and restrictions specified in this protocol
10. Parents or subjects' LAR able to give informed consent and willing and able to comply with all required study procedures. Assent is also required of children capable of understanding the nature of the study (typically ≥ 7 years old)

7.2 Subject Exclusion Criteria

1. History of seizures, other than febrile seizures, clinically significant cardiac arrhythmia, cystic fibrosis, 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. Use of rifampin within 14 days prior to study drug administration
3. Use of ranitidine, cimetidine, and antacids for subjects in Part B (oral administration) from 24 hours prior to study drug administration and throughout the study
4. Recent (3 month) history or current infection with viral hepatitis or other significant hepatic disease
5. History of drug allergy or hypersensitivity to oxazolidinones
6. Pregnant or breast feeding
7. Significant blood loss ($\geq 5\%$ of total blood volume) within 60 days before the Screening Visit
8. 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
9. Treatment with investigational medicinal product within 30 days before the infusion/dose of study drug
10. 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.)
11. Use of monoamine oxidase inhibitors or serotonergic agents including tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin 5 hydroxytryptamine receptor agonists (triptans), meperidine, or buspirone within, 14 days prior to study, or planned use while on study

7.3 Subject Withdrawal Criteria

7.3.1 Subject Withdrawal from the Study

Subjects may withdraw or be withdrawn from the study at any time. Subjects may be withdrawn from the study at the request of the Investigator or Sponsor. Reasonable efforts are to be made to complete all protocol-specified assessments listed for the Day 2 Visit at the time of withdrawal and to perform follow-up safety assessments.

7.3.2 Study or Site Discontinuation

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

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

8.0 TREATMENT OF SUBJECTS

8.1 Description of Study Drug

The investigational study drug is tedizolid phosphate (Sivextro), also known by the investigational number TR-701 FA, and will be supplied for IV infusion and as an oral suspension. Additional information is provided in Section 9.1 and a complete list of ingredients is provided in the Pharmacy Manual.

8.2 Concomitant Medications

Use of monoamine oxidase inhibitors or serotonergic agents including tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin 5-hydroxytryptamine receptor agonists (triptans), meperidine, or buspirone is not permitted while on study (refer to 19.0 Appendix E).

For subjects receiving oral tedizolid phosphate administration (Part B), ranitidine, cimetidine, and antacid use is prohibited.

8.3 Treatment Compliance

No calculations of treatment compliance are planned.

8.4 Randomization and Blinding

This is an open-label study with no randomization or blinding procedures.

9.0 STUDY DRUG MATERIALS AND MANAGEMENT

9.1 Study Drug Formulation/Packaging and Labeling/Storage

The investigational study drug is Tedizolid Phosphate, also known as Sivextro, MK-1986, and TR-701 FA.

Intravenous Form

Tedizolid Phosphate is formulated as a sterile lyophilized powder for injection for IV administration. Tedizolid Phosphate for Injection, 200 mg/vial, consists of Tedizolid Phosphate, mannitol, and sodium hydroxide that are lyophilized. 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 requirements. Additional information is provided in the Pharmacy Manual.

Oral 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 Type III glass bottles. Following constitution, each 1 mL contains 20 mg Tedizolid Phosphate. Inactive ingredients are potassium sorbate, silicon dioxide, succinic acid, sucrose and xanthan gum. Additional information is provided in the Pharmacy Manual.

Store all study drugs in accordance with instructions provided in the label on the clinical supply.

9.2 Administration

Subjects of 6 to <12 years will receive 4mg/ tedizolid phosphate; and subjects of 2 to < 6 years will receive 6 mg/kg (with possible adjustment based on the data from the second preliminary analyses of safety and PK) tedizolid phosphate as either an IV infusion (Part A) or an oral

suspension (Part B). Regardless of body weight, the maximum dose is 200 mg of tedizolid phosphate.

9.2.1 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.

9.2.2 Oral Tedizolid Phosphate

Oral tedizolid phosphate administration is to occur within 15-60 minutes following a meal. The target dose for oral administration is based on body weight using the following formula:

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

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

Volume required is provided in the Pharmacy Manual.

9.3 Study Drug Accountability, Handling, and Disposal

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

Additional information is provided in the Pharmacy Manual.

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

10.0 ASSESSMENT OF SAFETY

10.1 Safety Variables

Safety will be assessed through summaries of TEAEs, laboratory evaluations (hematology and chemistry), vital signs, physical examinations, and concomitant medications. Adverse events will be collected from the time when the ICF is signed through 7 days after study drug administration.

Clinical laboratory evaluations are listed in APPENDIX A. CLINICAL LABORATORY EVALUATIONS.

10.2 Assessing and Recording Adverse Events

10.2.1 Definition of 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 unfavorable 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 consent form is signed 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 7 days after study drug administration, 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 10.2.4.1. 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).

10.2.2 Definition of an Overdose for this Protocol and Reporting of an Overdose to the Sponsor

In this trial, an overdose is any dose higher than 1.25x times the nominal dose of tedizolid phosphate (nominal dose is 4 mg/kg daily for subjects 6 to <12 years, and 6 mg/kg for subjects 2 to <6 years, not to exceed the adult dose of 200 mg/day.) 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 post-natal day 7 through 54).

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 serious adverse event, even if no other seriousness 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 Event of Clinical Interest (ECI), 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).

10.2.3 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 7 days after study drug administration must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death,

intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

10.2.4 Immediate Reporting of Adverse Events to the Sponsor

10.2.4.1 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 another 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. Therefore, these events are considered serious by the Sponsor for collection purposes.

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

Refer to [Table 4](#) for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed 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 7 days after study drug administration, 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.

10.2.4.2 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 when the consent form is signed 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 7 days after study drug administration, 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 overdose of Sponsor's product, as defined in Section 10.2.2 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. 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).*

3. Severe or serious cases of *C. difficile* infection such as toxic megacolon or pseudomembranous colitis.
4. Clinically significant hematologic adverse events defined as hemoglobin <8.5 g/dL, platelet counts (<112 × 10³/mm³) or absolute neutrophil counts (<0.8 × 10³/mm³).
5. Serotonin syndrome in patients receiving drugs with serotonergic potential.

10.2.5 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in [Table 4](#). The investigator's assessment of causality is required for each adverse event. Refer to [Table 4](#) for instructions in evaluating adverse events.

Table 4 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 a Merck 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	
	† Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
† 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.)	

10.2.6 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.

11.0 ASSESSMENT OF PALATABILITY

Palatability will be assessed in subjects participating in Part B, oral administration, using a hedonic method (see APPENDIX B. PALATABILITY ASSESSMENT) and spontaneous verbal judgment.

12.0 PHARMACOKINETIC ASSESSMENT

12.1 Assessment

Plasma samples will be analyzed for concentrations of tedizolid phosphate and its active metabolite, tedizolid. Based on the individual plasma concentration-time data, using actual sampling times, PK parameters for tedizolid and tedizolid phosphate including the following will be determined:

- C_{max}
- t_{max}
- AUC
- $t_{1/2}$
- CL/F and CL, respectively

12.2 Samples

In Part A, blood samples for analysis of tedizolid phosphate and tedizolid will be collected at the following timepoints (shown in tabular format in [Table 5](#)):

6 years to <12 years of age: immediately after the end of the 1 hour infusion, and at 1.5, 2, 3, 4, 6, 12, and 24 hours after the start of infusion.

2 years to <6 years of age: immediately after the end of the 1 hour infusion, and at 3, 6, 12, 24, and 48 hours after the start of infusion (unless discharged after 24 hour sample)

In Part B, blood samples for analysis of tedizolid phosphate and tedizolid will be collected at the following timepoints:

6 years to <12 years of age: 1, 2, 3, 4, 6, 8, 12, and 24 hours after study drug administration.

2 years to <6 years of age: 3, 6, 9, 12, 24, and 48 hours after study drug administration (unless discharged after 24 hour sample)

Table 5 Pharmacokinetic sampling scheme.

		Time after start of infusion (hours)								
Part A (IV)	End of Infusion	1.5	2	3	4	6	12	24	48	
6 to <12 years	X	X	X	X	X	X	X	X		
2 to <6 years	X			X		X	X	X	X	
		Time after administration (hours)								
Part B* (Oral)	1	2	3	4	6	8	9	12	24	48
6 to <12 years	X	X	X	X	X	X		X	X	
2 to <6 years			X		X		X	X	X	X
Allowable windows on collection:										
Timepoint	<2 hours		2 to <6 hours		6 to 12 hours		24 hours		48 hours	
Window	±10 minutes		±15 minutes		±30 minutes		±2 hours		±2 hours	

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

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. 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.

Detailed instructions on collecting and processing blood PK samples are provided in APPENDIX C. PHARMACOKINETIC SAMPLING and the Laboratory Manual. Results of analysis will be reported separately.

13.0 STATISTICAL METHODS

13.1 Analysis Sets

The Intent to Treat (ITT) analysis set will consist of data from all enrolled subjects. Enrolled subjects include all subjects whose LAR signs the Informed Consent Form.

The Safety analysis set will consist of data from subjects who receive any study drug. Subjects will be categorized to the actual treatment received.

The PK analysis set will consist of data from subjects who receive study drug and have at least one quantifiable post-administration concentration.

13.2 Determination of Sample Size

No formal statistical tests are planned and the planned sample size is not based on a power calculation. Previous studies indicated that plasma tedizolid AUC has an intersubject percent coefficient of variation of approximately 20%.

If pediatric AUC is similar to adult AUC (Sivextro prescribing information 2015), then N=5 subjects per group affords 81% power to estimate group geometric mean AUC ratio and associated 90% confidence interval within the range of 0.5 to 2.0, which are boundaries that represent no clinically meaningful change for tedizolid plasma exposure (Flanagan 2014).

Six subjects will be enrolled per age group to assess bioavailability.

13.3 General Statistical Considerations

Continuous variables will be summarized with the number of subjects, mean, standard deviation, median, minimum, and maximum by age group and dose group. Categorical data will be summarized with the number and percentage in each category. All comparisons will be by age group and dose cohort.

Medical history and AEs will be coded using the MedDRA. Medications will be coded using the World Health Organization (WHO) Drug Dictionary to classify medications by preferred term and WHO Anatomical Therapeutic Chemical classification of ingredients.

Statistical summaries (descriptive statistics and frequency tables) will be generated using SAS[®] Version 9.3 or later (SAS Institute Inc., Cary, NC, USA). The statistical analysis plan will provide a detailed description of the statistical methods and will be finalized prior to database lock.

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

No formal statistical hypotheses testing will be performed. Therefore, multiplicity is not a concern.

13.3.1 Subject Enrollment and Disposition, and Protocol Violations/Deviations

Subject enrollment and disposition data will be summarized using all enrolled subjects in the eCRF database. This summary table will present the number of subjects who were enrolled in the study, received study drug, and completed the study for the ITT Analysis Set.

Protocol violations, deviations and inclusion/exclusion data will be summarized by age group and dose cohort by ITT Analysis Set

13.3.2 Study Drug Exposure

A study drug administration summary by age group and dose cohort will be provided including the distribution of the total number subjects receiving IV study drug, drug interruptions, and the number of oral administrations in the Safety Analysis Set.

Palatability assessments of oral suspension will be analyzed using descriptive statistics.

13.3.3 Demographics and Baseline Characteristics

Demographic data and baseline characteristics including medical history and pregnancy test results will be summarized for the Safety Analysis Set.

13.4 Pharmacokinetic Analysis

Descriptive statistics will be presented for tedizolid and tedizolid phosphate plasma concentrations by age group and dose cohort. Mean and individual plasma concentration-time profiles will be plotted in linear and semilogarithmic scales. All PK parameters will be summarized by age group and dose cohort using summary statistics.

The primary endpoint of the PK analysis is the geometric mean ratio of AUC (Part A Group 1 and Group 2) relative to adults, and bioavailability of tedizolid following oral tedizolid phosphate administration (Part B).

13.5 Safety Analysis

Safety will be assessed through summaries using descriptive statistics of TEAEs, laboratory evaluations, vital signs, physical examinations, and concomitant medications.

All safety analyses will be based on the Safety Analysis Set. Safety data will be summarized separately for each age group and dose cohort.

The number and percentage of subjects reporting will be presented by SOC and preferred term according to the MedDRA, by relationship to the study drug and by severity.

13.5.1 Adverse Events

All TEAEs will be recorded. Events with onset date that could not be used to determine its TEAE status or completely missing will be considered TEAEs. Treatment-emergent AEs, categorized by MedDRA system organ class and preferred term, will be summarized in tables. The tables will include the number of unique subjects experiencing each event, and percentage of subjects experiencing each event.

Treatment-emergent AEs will also be tabulated by the number and percentage of subjects experiencing events by severity and relationship to study drug. In the tabulation by severity, a

subject with more than 1 event coded to the same preferred term will be classified according to the most severe event. Similarly, in the tabulation by relationship, a subject will be classified according to the event with the strongest relationship to study drug.

Summaries of TEAEs leading to death and all SAEs will be provided. All reported AEs will be presented by site and subject in a data listing including the verbatim term, preferred term, and MedDRA SOC.

The safety evaluation will be based on clinical review of the following safety parameters:

- Incidence of AEs and SAEs
- AEs and SAEs by relationship to study drug
- AEs by severity
- Deaths
- Premature discontinuation from the study due to an AE, regardless of relationship to study medication
- Clinical laboratory data
- Vital signs
- Concomitant medications
- Physical examinations

13.5.2 Laboratory Evaluations

Hematology and chemistry laboratory data and vital signs data will be summarized using summary statistics. Changes from the Screening Visit to Day 2 will be summarized for laboratory data and vital signs parameters. The laboratory listings will provide a flag indicating all out-of-range laboratory assessments.

13.5.3 Prior and Concomitant Medications

Prior medications are any medication received prior to and stopped before the subject received study drug. Concomitant medications are any medication received by the subject starting on or after the day the subject received study drug, or given prior to the subject receiving study drug and continuing to receive it during the study. Only concomitant medications will be summarized. All medications will be presented in the listing.

13.6 Handling of Missing Data

Every effort should be made to collect all data at specified times, according to the schedule of study events. For all data points, missing data will be handled as follows:

- Missing values for individual data points will remain missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations
- Where individual data points are missing, categorical data will be summarized based on reduced denominators (i.e., only subjects with data available will be included in the denominators)

The handling of missing AE data, partial and missing dates are presented in detail in the statistical analysis plan.

14.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1 Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Sponsor will visit the investigational study site to determine the adequacy of the facilities and discuss with the Investigator(s) and other personnel their responsibilities and the responsibilities of Sponsor or its representatives. This will be documented in a Clinical Study Agreement between Sponsor and the investigator.

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, e.g., data are being accurately recorded in the e-CRF, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRF with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts)
- Record and report any protocol deviations not previously sent to Sponsor
- Confirm AEs and SAEs have been properly documented on e-CRFs and confirm any SAEs have been forwarded to Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB

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

Sponsor personnel or their designee may perform an audit at any time during or after completion of the clinical study, as defined in the Audit Plan. All study-related documentation is to be made available to the designated auditor. In addition, study site personnel are to be available to answer any questions. The Investigator will permit authorized representatives of the Sponsor and the regulatory agencies or local health authorities to inspect facilities and records relevant to this study.

14.1.1 Protocol Violations and Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Deviations include, but are not limited to, the following:

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

15.0 ETHICS

15.1 Ethics Review

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

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

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

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

15.2 Written Informed Consent

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

The Investigator or designee is to explain the study and ICF to the subject and answer any questions in accordance with 21 CFR Part 50. The person who conducts the informed consent/assent discussion is to sign and date the ICF and provide a fully executed copy to the subject. If applicable, an IRB approved certified translation of the ICF in a language understandable to the subject will be provided.

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

15.3 Subject Confidentiality

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

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

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

16.0 DATA HANDLING AND RECORDKEEPING

16.1 Case Report Forms and Study Records

The site will use a web browser address for an Electronic Data Capture system database that has been fully validated and conforms to 21 CFR Part 11 and the Guidance for Industry on Computerized Systems Used in Clinical Trials requirements. This study will be performed using an e-CRF. The Investigator and study site staff will receive training and support on the use of the e-CRF. All e-CRF data are to be completed by the study coordinator or other designated site personnel. All data entry, modification, or deletion will be recorded automatically in the electronic audit trail. All data changes will be clearly indicated with a means to locate prior values. Informed consent, demography, inclusion/exclusion and end of study e-CRF pages are needed for patients who are enrolled but not treated.

All electronic data entered by the site (including the electronic audit trail) will be maintained or made available at the site in compliance with 21 CFR Part 11 and other applicable retention regulations. The computerized system is able to generate accurate and complete copies of records in paper or electronic form for inspection and review by applicable regulatory authorities, the IRB, and auditors or other designees authorized by Sponsor.

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

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

16.2 Data Quality Assurance

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

Audits for quality assurance of the database may be performed according to relevant procedures within the research organization or at the request of Sponsor's Quality Assurance department.

16.3 Inspection of Records

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

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

16.4 Retention of Records

The Investigator is to retain records and documents pertaining to the conduct of this study including PDF copies of e-CRFs, source documents, ICFs, laboratory test results, and study medication inventory records for a period of at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. No study records shall be destroyed without prior authorization from the Sponsor.

17.0 PUBLICATION POLICY

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

18.0 LIST OF REFERENCES

Sivextro™ US Prescribing Information. Merck & Co., 2015. Accessed: Feb 2016.
Available from: http://www.merck.com/product/usa/pi_circulars/s/sivextro/sivextro_pi.pdf

Flanagan S, Passarell J, Lu Q, Fiedler-Kelly J, Ludwig E, Prokocimer P. Tedizolid Population Pharmacokinetics, Exposure Response, and Target Attainment. *Antimicrob Agents Chemother.* 2014;58(11):6462-70.






19.0 APPENDICES

APPENDIX A. CLINICAL LABORATORY EVALUATIONS

Clinical Laboratory Evaluations	
<p>Chemistry Panel Total Bilirubin Direct Bilirubin Indirect Bilirubin Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Gamma-glutamyl transpeptidase Lactate dehydrogenase Urea nitrogen Creatinine Glucose Uric Acid Calcium Phosphorus Total Protein Cholesterol Creatine kinase/creatine phosphokinase Sodium Potassium Bicarbonate Chloride Magnesium</p>	<p>Hematology/Differential Panel Hemoglobin Hematocrit Red blood cell count White blood cell count Neutrophils (% absolute) Lymphocytes (% absolute) Monocytes (% absolute) Eosinophils (% absolute) Basophils (% absolute) Bands (% absolute), if available Platelet count</p> <hr/> <p>Pregnancy Test (females of childbearing potential in Groups 1 and 3); Serum or urine beta-human chorionic gonadotropin (If urine test is used, it must be high sensitivity [i.e. able to detect 10 mIU/mL hCG])</p> <hr/> <p>Urine Panel (Screening only) pH Bilirubin Glucose Ketones Urobilinogen</p>

APPENDIX B. PALATABILITY ASSESSMENT

Palatability will be evaluated using a 5-point hedonic scale in subjects administered tedizolid phosphate oral suspension, using the tool shown below. The facial score should be rated by the child, in verbal children of an age able to understand. (Ask the subject to rate the taste of tedizolid phosphate suspension. The subject can respond orally and/or by pointing to a face). For preverbal children, the score should be assessed by the parent/caregiver, or study staff administering or witnessing administration of the study drug.

This form should be completed at the time of oral medication administration. Please answer all questions.				
1. Please mark the box of one picture below to show how you/the child feels about the taste of the medication:				
				
<input type="checkbox"/> Very bad	<input type="checkbox"/> Bad	<input type="checkbox"/> Neither good nor bad	<input type="checkbox"/> Good	<input type="checkbox"/> Very good
2. Please mark one box below to identify the person entering the responses on the questionnaire.				
<input type="checkbox"/> Reported by the patient	<input type="checkbox"/> Observed by a parent/primary caregiver			
<input type="checkbox"/> Observed by a nurse	<input type="checkbox"/> Observed by another health care provider (e.g.: physician, medical assistant or nursing assistant caring for the patient)			
3. Please indicate if you/the child had any of the following problems when taking the medication by mouth:				
a. Refusing	<input type="checkbox"/> Yes	<input type="checkbox"/> No		
b. Spitting Out	<input type="checkbox"/> Yes	<input type="checkbox"/> No		
c. Vomiting or Spitting Up	<input type="checkbox"/> Yes	<input type="checkbox"/> No		
d. Gagging	<input type="checkbox"/> Yes	<input type="checkbox"/> No		
e. Other, specify	<input type="checkbox"/> Yes	<input type="checkbox"/> No	_____	
4. Are there any other comments related to the taste of the medication? <input type="checkbox"/> Yes <input type="checkbox"/> No				
Specify comments: _____				

Facial score from Sjøvall J, Fogh A, Huitfeldt B, Karlsson G, Nylén O. Methods for evaluating the taste of paediatric formulations in children: A comparison between the facial hedonic method and the patients' own spontaneous verbal judgment. *Eur J Pediatr.* 1984;141(4):243-7.

APPENDIX C. PHARMACOKINETIC SAMPLING

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

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. 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.

Detailed information on sample collection and processing is provided in the Laboratory Manual. Perform the following:

1. Collect blood (500 μ L) in the tube provided by the Sponsor-designated central laboratory
2. Slowly invert the tube at least 8 to 10 times
3. Place the tube in an ice water bath until centrifugation
4. Centrifuge the sample at $2000 \times g$ at 5°C for 15 minutes. If a refrigerated centrifuge is not available, place the tube in an ice bath immediately before and after the centrifugation for at least 5 minutes each time
5. Collect supernatant (plasma) and split into 2 aliquots and store at -20°C or colder
 - One aliquot will be shipped to the Sponsor-designated central laboratory
 - The other aliquot is to be stored at the study site as a back-up sample until notified by Sponsor or designee that the sample either is to be sent to the Sponsor-designated central laboratory or is to be destroyed

APPENDIX D. SCHEDULE OF STUDY ASSESSMENTS

Assessment	Screening^a (Study Day -3 to 1)	Study Day 1	Study Day 2	Study Day 8 (±1 day; may be phone contact)
Informed Consent/Assent (before study)	X			
Verify subject meets eligibility criteria	X			
Record demographic data and medical history (up to last 5 years)	X			
Perform 12-lead electrocardiogram ^b	X			
Record vital signs	X	X ^c	X	
Record height and weight	X			
Perform physical examination	X		X	
Record prior and concomitant medications	X	X		X
Administer study drug ^d		X		
Conduct palatability test ^e		X		
Assess adverse events (collected from signed ICF through 7 days after administration)	X	X	X	X
Perform HDYF inquiry ^f	X	X	X	
Collect blood samples for PK analysis ^g		X	X	
Collect urine and blood samples for urinalysis and chemistry and hematology analyses ^h	X ⁱ	X (only if Screening Visit sample >7 days prior)	X (blood sample only)	
Collect blood or urine sample for pregnancy test ^j	X			

Abbreviations: HDYF=how do you feel; ICF=informed consent form; IV=intravenous; PK=pharmacokinetic

^a Screening procedures may be completed on Day 1.

^b Subjects will rest in the supine position 10 minutes prior to ECG recording, ECGs collected within 30 days prior to screening may be used to satisfy the screening requirement. If more than one ECG is available within the 30 days window, the most recent ECG should be used to satisfy the screening requirement.

^c For Day 1, record vital signs (including temperature, respiratory rate, and resting blood pressure and pulse) prior to study drug administration. Also record resting blood pressure and pulse at 0.5, 1, 2, 3, 4, and 6 hours after study drug administration (relative to the start of infusion for IV administration). The consistent method should be used to measure body temperature, and the subject should be in the same position (e.g. supine) for all vital sign measurements.

^d Administer tedizolid phosphate as a 60-minute IV infusion (Part A) or oral suspension (Part B). Oral tedizolid phosphate administration is to be given within 15-60 minutes following a meal

^e Palatability will be assessed following oral suspension administration (Part B).

^f HDYF inquiry performed at vital signs measurement, once daily.

^g Samples are to be collected at timepoints as described in Section 12.2.

^h Laboratory evaluations include serum chemistry and hematology panels, and urinalysis.

ⁱ Pre-screening local laboratory test results that were collected as part of standard of care may be used if collected within 7 days prior to the dose of study medication.

^j Females of childbearing potential in Groups 1 and 3 only. If urine test is used, it must be high sensitivity (i.e. able to detect 10 mIU/mL hCG).

APPENDIX E. Examples of Prohibited Concomitant Medications

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

Receipt of the following medications is prohibited in the 2 weeks prior to study through the last visit.

Examples		
Monoamine Oxidase Inhibitors		
Iprindole	Moclobemide	Rasagiline
Iproniazid	Nialamide	Selegiline
Iproclozide	Opipramol	Toloxatone
Isocarboxazid	Phenelzine	Tranlycypromin
Selective Serotonin Reuptake Inhibitors		
Citalopram	Fluoxetine	Sertraline
Dapoxetine	Fluvoxamine maleate	Vilazodone
Escitalopram oxalate	Paroxetine	
Serotonin Norepinephrine Reuptake Inhibitors		
Duloxetine	Desvenlafaxine	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	

20.0 SIGNATURE

Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	