sNDA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplements
Application Number(s)	NDA 205435/S-016 SIVEXTRO (tedizolid phosphate) tablet NDA 205436/S-013 SIVEXTRO (tedizolid phosphate) for injection
Priority or Standard	Standard
Submit Date(s)	June 6, 2024
Received Date(s)	June 6, 2024
PDUFA Goal Date	April 6, 2025
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	See electronic signature page
Established/Proper Name	Tedizolid phosphate
(Proposed) Trade Name	SIVEXTRO
Pharmacologic Class	Oxazolidinone Antibacterial
Applicant	Cubist Pharmaceuticals LLC, a subsidiary of Merck & Co., Inc.
Dosage form	Tablet and Injection
Applicant proposed Dosing Regimen	**Adult and pediatric patients weighing ≥35 kg:** 200 mg tedizolid phosphate administered once daily as an intravenous (IV) infusion over 1 hour or orally as an oral tablet for 6 days. **Pediatric patients weighing less than 35 kg:** Tedizolid phosphate dose determined by patient body weight administered twice daily as an IV infusion over 1 hour for 6 days, as follows: • (b) (4) • Body weight 3 to <6 kg: 12 mg • Body weight 6 to <10 kg: 20 mg • Body weight 10 to <14 kg: 30 mg • Body weight 14 to <20 kg: 40 mg • Body weight 20 to <35 kg: 60 mg
Applicant Proposed Indication(s)/Population(s)	Pediatric patients from (b) (4) to less than 12 years of age for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin susceptible [MSSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis* [Already approved for

	use in patients 12 years of age and older for the same indication.]
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis* in adult and pediatric patients (at least 26 weeks gestational age and weighing at least 1 kg).
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Bacterial infection of skin (disorder) SCTID: 128936008
Recommended Dosing Regimen	**Adult and pediatric patients weighing ≥ 35 kg:** 200 mg tedizolid phosphate administered once daily as an intravenous (IV) infusion over 1 hour or orally as an oral tablet for 6 days. **Pediatric patients (at least 26 weeks gestational age) weighing from 1 kg to < 35 kg:** Tedizolid phosphate dose determined by patient body-weight administered twice daily as an IV infusion over 1 hour for 6 days, as follows: • Body weight 1 to <2 kg: 3 mg/kg • Body weight 2 to <3 kg: 6 mg • Body weight 3 to <6 kg: 12 mg • Body weight 6 to <10 kg: 20 mg • Body weight 10 to <14 kg: 30 mg • Body weight 14 to <20 kg: 40 mg • Body weight 20 to <35 kg: 60 mg

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DMPP/PLT Reviewer and Team Leader	Mary Carroll; Marcia Williams
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OPDP=Office of Prescription Drug Promotion
DMPP= Division of Medical Policy Programs
PLT=Patient Labeling Team
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

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Signature: {See appended electronic signature page}

Glossary

ABSSSI	acute bacterial skin and skin structure infections
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
APaT	All Participants as Treated
AUC_{0-24}	area under the curve over 24 hours
BCRP	breast cancer resistance protein
BLA	biologics license application
BLQ	below limit of quantification
CE	clinically evaluable
CE-TOC	clinically evaluable at test of cure
CL	clearance
C_{max}	maximum concentration
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
DMC	data monitoring committee
EOT	end of treatment

*f*AUC	free drug AUC
FDA	Food and Drug Administration
FLACC	Face, Legs, Activity, Cry, Consolability
GI	gastrointestinal
GOF	goodness-of-fit
IIV	interindividual variability
ITT	intent-to-treat
Ka	absorption rate constant
MedDRA	Medical Dictionary for Regulatory Activities
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
MITT	microbiological intent-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NDA	new drug application
NHANES	National Health and Nutrition Examination Survey
OCP	Office of Clinical Pharmacology
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
pcVPC	Prediction-corrected VPC
PI	prescribing information
PK/PD	pharmacokinetic/pharmacodynamic
PMR	postmarketing requirement
popPK	population PK
PREA	Pediatric Research Equity Act
PTA	probability of pharmacokinetic pharmacodynamic target attainment
RSE	relative standard error expressed as a percent
RV	residual variability
SAE	serious adverse event
sNDA	supplemental new drug application
SOC	system organ class
TEAE	treatment-emergent adverse event
TOC	test of cure
Vc	central volume of distribution
VPC	visual predictive check

1. Executive Summary

1.1. Product Introduction

Tedizolid phosphate (SIVEXTRO) is a member of the oxazolidinone class of antibacterial drugs and is a prodrug that is rapidly converted in vivo by phosphatases to the active moiety, tedizolid. Tedizolid acts by binding to the 50s subunit of the bacterial ribosome, resulting in inhibition of protein synthesis. Tedizolid phosphate is currently approved in adults and adolescent patients (12 years to less than 18 years of age) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus* [MRSA] and methicillin-susceptible *Staphylococcus aureus* [MSSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis*. Tedizolid phosphate is available as 200 mg strength tablets for oral administration or as a sterile lyophilized powder for injection in single-dose vials (200 mg/vial). The recommended dosage in both adults and adolescents is 200 mg administered once daily for 6 days either orally (with or without food) or as an intravenous (IV) infusion over 1 hour.

These supplemental new drug applications (sNDAs) propose to extend the currently approved ABSSSI indication for tedizolid phosphate in adult and adolescent patients to include the pediatric population less than 12 years of age. The currently approved oral and IV dosage in adult and adolescent patients (200 mg once daily for 6 days, either as an oral tablet or as an IV infusion over 1 hour, for 6 days) is proposed for use in all pediatric patients weighing ≥35 kg, regardless of age. (b) (4), the Applicant proposes weight-banded IV dosing of tedizolid phosphate with twice daily administration as an IV infusion over 1 hour for 6 days.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The substantial evidence of effectiveness to support the approval of tedizolid phosphate for treatment of ABSSSI in pediatric patients aged (b) (4) (at least 26 weeks gestational age and weighing at least 1 kg) to less than 12 years was extrapolated from adequate and well-controlled trials of tedizolid phosphate in adults for the same indication. Extrapolation is supported by the similarities in the pathophysiology of the infection as well as exposure comparisons (pharmacokinetic model-based analyses) between pediatric patients aged birth to less than 12 years of age at the proposed dosages and adult patients receiving the approved dosage. Supportive evidence of effectiveness in pediatric patients less than 12 years of age is provided by Study MK-1986-018, a randomized, active-controlled, single-blind, multicenter

study that evaluated safety and efficacy of IV and/or oral tedizolid phosphate treatment for ABSSSI in pediatric patients aged 4 months to less than 12 years.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Tedizolid phosphate is currently approved for IV and oral (tablet) use in adults and adolescent patients (12 years to less than 18 years of age) for the treatment of ABSSSI caused by designated susceptible bacteria. In these sNDAs, the Applicant is seeking to expand the indication for IV use to include pediatric patients aged (b) (4) to <12 years, and for use of the oral tablet in pediatric patients aged <12 years and weighing ≥ 35 kg. The Applicant has conducted a randomized (3:1), multicenter, investigator-blinded, safety and efficacy study of tedizolid phosphate for 6 to 10 days versus comparator therapy for 10 to 14 days for the treatment of suspected or documented gram-positive ABSSSI in 100 pediatric subjects 4 months to less than 12 years of age. Additionally, the Applicant also conducted an open-label pharmacokinetic and safety trial enrolling 47 pediatric patients less than 2 years of age.

While there were no primary efficacy endpoints in the ABSSSI pediatric Study MK-1986-018, the secondary efficacy endpoint was clinical response (per the blinded investigator's assessment) at the Test-of-cure (TOC) visit (22-29 days after first dose of study drug) in the intent-to-treat (ITT) and clinically evaluable (CE) populations. Clinical success rates in the ITT population at the TOC visit were 70/75 (93.3%) in the tedizolid arm versus 23/25 (92%) in the comparator arm, with a treatment difference of 1.3%. In the clinically evaluable at test of cure (CE-TOC) population, success rates were 68/68 (100%) versus 23/23 (100%), with no treatment difference. These findings were robust to the choice of analysis sets and time points. Findings in other efficacy endpoints were supportive of the primary analysis findings. Exposure data from this study and the open-label PK study in pediatric patients less than 2 years of age were utilized in the PK model-based analysis to determine appropriate dosing for pediatric patients down to birth.

The most common adverse reactions in pediatric patients treated with tedizolid in Study MK-1986-018 were infusion- or injection-related adverse reactions (5%) and vomiting (4%). There were no deaths, and no serious adverse events were related to tedizolid administration. The safety profile of tedizolid in pediatric patients less than 12 years of age was comparable to that of adults and adolescents. Use of tedizolid for the treatment of ABSSSI is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric subjects less than 12 years of age. Availability of tedizolid for use in pediatric subjects less than 12 years of age will add to the armamentarium of products available for the treatment of ABSSSI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ABSSSI include cellulitis/erysipelas, wound infections, and major cutaneous abscesses, which are most commonly caused by *Staphylococcus aureus* and beta-hemolytic streptococci in pediatric and adult patients worldwide. ABSSSI caused by resistant organisms, particularly MRSA, are of increasing concern due to the limited treatment choices. ABSSSI are seen in all pediatric age groups. The profile of causative ABSSSI pathogens is the same for pediatric, adolescent and adult infections. The severity of illness ranges from mild to severe infections.	• ABSSSI are common, serious bacterial infections that can cause significant morbidity.
Current Treatment Options	• There are many therapies available for treatment of ABSSSI due to gram positive organisms, including linezolid, daptomycin, clindamycin, cefazolin, ampicillin/sulbactam, ceftriaxone, cefotaxime, trimethoprim/sulfamethoxazole, doxycycline, omadacycline, telavancin, tigecycline, oritavancin, dalbavancin, ceftaroline and vancomycin. However, several of these antibacterial therapies are limited by their toxicities and the development of antibacterial resistance. • Oral antibacterial options for treating ABSSSI in patients with community-associated MRSA include clindamycin, trimethoprim/sulfamethoxazole, tetracyclines, and linezolid. • For hospitalized children, vancomycin or clindamycin (if resistance rates are low), may be used when MRSA is a concern.	• Choice of antibacterial therapy for ABSSSI is usually dictated by host factors (risk factors for particular organisms or state of immunosuppression), local resistance profile, and severity of disease. • Availability of tedizolid for use in pediatric patients less than 12 years of age will add to the armamentarium of products available for ABSSSI.
Benefit	• Study MK-1986-018 is a 3:1 randomized, multicenter, safety and efficacy study of tedizolid phosphate (weight-based dosing of IV and/or oral for 6 to 10 days) versus comparator therapy (IV and/or orally for 10 to 14 days) for the treatment of suspected or documented gram-positive ABSSSI in 100 subjects from 4 months to	• Use of tedizolid for the treatment of ABSSSI is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric subjects aged from (b) (4) to less

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	less than 12 years of age. The comparators included vancomycin, cefazolin, linezolid, clindamycin, and others. • The secondary efficacy endpoint was clinical response (per the blinded investigator's assessment) at the TOC visit (22-29 days after the first dose of study drug) in the ITT and CE populations. • An additional efficacy endpoint was early clinical response at the 48-to-72-hour visit (≥20% reduction of lesion area from baseline). • Clinical success rates in the ITT population at the TOC visit were 70/75 (93.3%) in the tedizolid arm versus 23/25 (92%) in the comparator arm, with a treatment difference (tedizolid minus comparator) of 1.3% (95% CI: -10.7, 13.4). • Responder rates at the 48-to72-hour visit were 80% in the tedizolid arm vs. 84% in the comparator arm, a difference of -4% (95% CI: -21, 13). • Exposure data from this study and an open-label PK study in pediatric subjects down to birth were utilized in the PK model-based analysis to determine appropriate dosing for pediatric patients down to birth.	than 12 years. • Study MK-1986-018 showed a high rate of clinical success at the TOC visit which was similar in the tedizolid and comparator arms. Findings with other efficacy endpoints were supportive. Results from this trial support the efficacy of tedizolid in the treatment of ABSSSI in pediatric subjects.
Risk and Risk Management	• Safety concerns associated with the oxazolidinone drug class include myelosuppression, serotonin syndrome, optic neuropathy, lactic acidosis, peripheral neuropathy, drug interactions between oral tedizolid and oral breast cancer resistance protein (BCRP) substrates, and *Clostridiodes difficile*-associated diarrhea. • The safety population in Study MK-1986-018 included 100 subjects, 75 treated with tedizolid and 25 treated with comparators with no deaths or serious adverse events deemed related to tedizolid. • The Applicant also conducted MK-1986-014, an open-label pharmacokinetic and safety trial that enrolled 47 pediatric patients	• The safety profile of tedizolid in pediatric subjects less than 12 years of age is comparable to that of adults and adolescents. • Risks have been adequately conveyed in the labeling. No additional risk mitigation strategies are needed at this time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	less than 2 years of age that had a comparable safety profile. • Treatment-emergent adverse events (TEAEs) in the tedizolid arm (28%) were slightly higher than in the comparator arm (24%). • The most common adverse reactions in pediatric subjects receiving tedizolid included infusion- or injection-related adverse reactions (5%) and vomiting (4%). • The safety profile in pediatric patients less than 4 months down to birth was similar to that observed in older pediatric patients and adults.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

ABSSSI include cellulitis/erysipelas, wound infections, and major cutaneous abscesses. *S. aureus* is the most common cause of ABSSSI encountered in the outpatient or inpatient setting. Among outpatients presenting with purulent ABSSSI to emergency rooms in the US, *S. aureus* accounts for approximately 76%, with MRSA accounting for approximately 59% (Talan et al. 2011). Among inpatients, *S. aureus* accounts for approximately 70% of cutaneous abscesses and ABSSSI with additional complicating factors, of which MRSA accounts for approximately 45% (Jenkins et al. 2010). ABSSSI range in severity from mild, localized infections to severe infections with signs and symptoms of systemic toxicity. Currently, ABSSSI are one of the most common infections leading to hospitalization. Mortality due to untreated ABSSSI in the current era is unknown, but prior to the advent of antibacterial therapy, mortality due to cellulitis/erysipelas was estimated at 10-11% and at 5-8% due to carbuncles and furuncles (Spellberg et al. 2009). Among pediatric groups, ABSSSI are seen from premature infants to teenagers, without predilection for a particular age subset. The profile of causative ABSSSI pathogens is the same across pediatric, adolescent and adult infections.

2.2. Analysis of Current Treatment Options

Available FDA-approved and -unapproved therapies for ABSSSI include linezolid, daptomycin, clindamycin, cefazolin, ampicillin-sulbactam, ceftriaxone, cefotaxime, ertapenem, levofloxacin, meropenem, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, doxycycline, omadacycline, telavancin, tigecycline, oritavancin, dalbavancin, ceftaroline, and vancomycin. For hospitalized children, vancomycin or clindamycin may be used when MRSA is a concern. For β-hemolytic streptococci, penicillin or clindamycin can be used in pediatric patients. Oral antibacterial options for treating skin and soft-tissue infections in patients with community-associated MRSA include clindamycin, trimethoprim-sulfamethoxazole, tetracyclines, and linezolid.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Sivextro (tedizolid phosphate) tablet and injection received FDA approval on June 20, 2014, for treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult patients. At the time of approval, five pediatric studies under the Pediatric Research Equity Act (PREA) were

required:

- A randomized comparative safety and efficacy study of IV and oral tedizolid for the treatment of ABSSSI in pediatric patients aged from 12 to <18 years (postmarketing requirement (PMR) 2159-1)
- A randomized comparative safety and efficacy study of IV and oral tedizolid for the treatment of ABSSSI in pediatric patients aged >3 months to < 12 years (PMR 2159-2)
- An open-label of IV tedizolid for hospital-acquired late onset sepsis in full term and preterm neonates and infants aged 5 days to < 3 months (PMR 2159-3).
- A phase 1 single-dose safety and PK study of oral and IV tedizolid in patients 2 years to < 12 years of age (PMR 2159-4)
- A phase 1 single-dose safety and PK study of oral and IV tedizolid in patients under 2 years old (PMR 2159-5)

On January 29, 2018, PMR 2159-2 and PMR-2159-3 were released and a new pediatric requirement for a randomized comparative trial to assess the safety and efficacy of IV and oral tedizolid for the treatment of ABSSSI in pediatric patients aged birth to < 12 years was issued (PMR 2159-7).

On January 15, 2020, the Agency issued a fulfillment of postmarketing requirement letter for PMR 2159-4.

On June 19, 2020, two Prior Approval Supplements, NDA 205435/S-012 and NDA 205436/S-007, were approved expanding the treatment of ABSSSI to patients from 12 years to less than 18 years of age, fulfilling PMR 2159-1.

This submission fulfills PMR 2159-5 and PMR 2159-7 and will expand the approval of tedizolid for the treatment of ABSSSI to pediatric patients from (b) (4) to 12 years of age.

3.2. Summary of Presubmission/Submission Regulatory Activity

On June 6, 2024, Prior Approval Efficacy Supplements, NDA 205435/S-016 and NDA 205436/S-013, were submitted to expand the currently approved adult and adolescent indication for Sivextro (tedizolid phosphate) tablet to include dosing recommendations for pediatric patients ≥35 kg and to expand the currently approved adult and adolescent indication for Sivextro (tedizolid phosphate) for injection to include pediatric patients from (b) (4) to <12 years of age. With these submissions, the Applicant is requesting the fulfillment of PMRs 2159-5 and 2159-7 as the final study reports for these PMRs were submitted to the respective NDAs for IV and oral tedizolid. S-013 and S-016 were filed on August 14, 2024. The Prescription Drug User Fee Act goal date for the Prior Approval Supplements is April 6, 2025.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

There were no issues identified regarding data quality and integrity for Study 018. OSI did not inspect any study sites for Study MK-1986-018.

OSI investigated clinical sites for two phase 1 studies, one in pediatric subjects 2 to < 12 years old and the other in pediatric subjects under 2 years old to ensure data quality and protocol safety. Three sites were chosen, one in Orange, California in the USA and two international sites: Bergen, Norway and Barranquilla, Atlantico, Colombia. OSI did not identify any concerns regarding reliability of the data or objectionable conditions. For further details, please refer to the clinical inspection summary written by Dr. Monica Javidnia from OSI, dated February 10, 2025, uploaded in DARRTS.

4.2. Product Quality

Sivextro (tedizolid phosphate) is currently available in 200 mg tablets and 200 mg powder for injection for the treatment of ABSSSI. The currently approved drug product formulations are used for the proposed indication, so no new quality chemistry, manufacturing, and controls information was included in the current submission (Please see reviews CMC - NDA-205435-SUPPL-16.docx, dated November 25, 2024, and CMC - NDA-205436-SUPPL-13.docx, dated November 21, 2025, in Panorama for details).

4.3. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The current sNDAs are intended to extend approval of tedizolid to pediatric patients from (b) (4) up to 12 years of age. In addition to clinical studies conducted in pediatric subjects, two juvenile toxicology studies completed in Sprague Dawley and Long Evans rats are supportive of the sNDAs.

Dosing in both juvenile toxicology studies began on postnatal day 7 (PND 7) and extended through PND 56 with the same orally administered dosages of tedizolid phosphate in both studies. A tedizolid-related finding with possible clinical relevance in both studies, mortality and morbidity, occurred in multiple high-dose animals receiving an initial dose of 10 mg/kg/day of tedizolid phosphate. All the unscheduled deaths in both studies occurred at about the time of weaning from PND 17 to PND 24 in Sprague Dawley rats and from PND 21 to PND 28 in Long Evans rats. Clinical signs observed in the prematurely deceased animals included pale body, cool or pale extremities, partial closure of the eyes, increased respiration, shallow respiration, prostration, hypoactivity, gasping, and dermal atonia. Mortality and clinical signs were not apparent in older and younger rats in the high-dose group suggesting juvenile rats were only susceptible to tedizolid-related adverse effects during a particular period of development at or near weaning. Age-related changes in tedizolid plasma exposures may have influenced the pattern of tedizolid-related toxicities. Dose-normalized tedizolid exposures were highest on PND 7 with lower values occurring as animals matured. The plasma exposure associated with the 10 mg/kg/day dose in Sprague Dawley rats on PND 7 was approximately 150 mcg•hr/ml which is approximately 4-7 times the expected plasma exposure (range of 20.84 to 38.70 mcg•hr/ml) in pediatric patients aged newborn to less than 18 years receiving multiple administrations of tedizolid phosphate in the recommended daily dosages.

The age-related changes in plasma exposure in the juvenile rats are also a finding with possible clinical relevance. For reasons not completely understood, tedizolid plasma exposures decreased as animals matured. Plasma exposures were higher on PND 7, the first day of dosing, than on PND 35 after the weaning period. On PND 43, daily dosages of tedizolid phosphate were increased four-fold in males and two-fold in females. Following the increases in daily dosages, the mean plasma AUC exposures on PND 56 were similar to those on PND 7 suggesting changes in tedizolid metabolism or clearance occurred as the rats matured which resulted in substantially lower dose-normalized exposures. The precise mechanisms underlying the changes in tedizolid exposure were not elucidated, but clinical pharmacokinetic data suggests the potential for similar although more muted changes in exposure in humans. In clinical studies, tedizolid exposures were approximately 1.4-fold higher in pediatric patients 12 to < 18 years of age compared to adult patients.

An important negative finding in the juvenile toxicology studies is that administration of tedizolid phosphate was not associated with adverse neurological or ophthalmic effects. Other oxazolidinone drugs have been associated with peripheral and optic neuropathy. Tedizolid was not associated with these effects in adult rats and negative findings for neurological and ophthalmoscopy evaluations for both strains of rats in the juvenile studies suggests no greater potential in juvenile rats.

Based on the results in the juvenile rat studies, the sNDAs for tedizolid phosphate administration to pediatric ABSSSI patients from (b) (4) up to 12 years of age is considered approvable from a Pharmacology/Toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

INDs 77872 and 106307

5.3. Pharmacology

The secondary and safety pharmacology studies and the absorption, distribution, metabolism, and excretion (ADME)/PK studies and toxicokinetic results for the general toxicology and reproductive and developmental toxicology studies conducted with tedizolid phosphate (TR-701 FA) are reviewed in the 2014 Pharmacology/ Toxicology review for NDAs 205435 and 205436 by James Wild, PhD. The toxicokinetic results summarized in Section 5.4 below are those associated with the juvenile toxicology studies conducted with TR-701 FA in rats.

5.4. ADME/PK

Table 1. ADME/PK and Toxicokinetics

Type of Study	Major Findings
Toxicokinetic data from general toxicology studies	
50-Day, Oral Gavage, Toxicology Study with TR-701 FA in Juvenile Sprague-Dawley Rats/ Study No: TE.701.TX.002 **Initial Doses for Males and Females (PND 7 to PND 42):** 0 (vehicle), 1 mg/kg/day (Group); 3 mg/kg/day (Group 3); and	**Sex differences:** No sex-related differences in AUC_{0-t} or C_{max} values for TR-700 were observed on PND 7. By PND 35, however, AUC_{0-t} and C_{max} values were 1.4 to 3.3-fold greater in females compared to males. **Time-dependent changes in exposure:** Plasma AUC_{0-t} values for TR-700 on PND 35 were approximately 4.1- to 8.0-fold lower for males and 1.1- to 2.3-fold lower for females compared to PND 7. After 4-fold and 2-fold dose increases on PND 43 in males and females, respectively, plasma AUC_{0-t} values on PND 56 were comparable to those observed on PND 7 in both sexes.

Type of Study	Major Findings
10 mg/kg/day (Group 4) **Developmental Doses for Males (PND 43 to PND 56):** 0 (vehicle), 4 mg/kg/day (Group 2); 12 mg/kg/day (Group 3); and 40 mg/kg/day (Group 4) **Developmental Doses for Females (PND 43 to PND 56):** 0 (vehicle), 2 mg/kg/day (Group 2); 6 mg/kg/day (Group 3); and 20 mg/kg/day (Group 4)	**Accumulation:** Dose-normalized plasma AUC values decreased with the age of the rats. There was no evidence of accumulation in either sex. **Dose proportionality:** TR-700 plasma exposure (AUC_{0-t}) values were approximately dose proportional (within 2-fold) for both male and female rats on PNDs 7, 35, and 56. **Table 2. Mean Plasma Values for TR-700 Toxicokinetic Parameters in Male Sprague Dawley Rats on PNDs 7, 35, and 56.** Group 2: 1 mg/kg, PND 7, AUC_{0-t} 13.1 mcg•hr/ml, Dose-Norm AUC_{0-t} 13.1, C_{max} 0.912 mcg/ml, Dose-Norm C_{max} 0.912, T_{max} 6 h Group 2: 1 mg/kg, PND 35, AUC_{0-t} 2.83 mcg•hr/ml, Dose-Norm AUC_{0-t} 2.83, C_{max} 0.954 mcg/ml, Dose-Norm C_{max} 0.954, T_{max} 1 h Group 2: 4 mg/kg, PND 56, AUC_{0-t} 10.9 mcg•hr/ml, Dose-Norm AUC_{0-t} 2.73, C_{max} 4.11 mcg/ml, Dose-Norm C_{max} 1.03, T_{max} 1 h Group 3: 3 mg/kg, PND 7, AUC_{0-t} 38.3 mcg•hr/ml, Dose-Norm AUC_{0-t} 12.8, C_{max} 2.64 mcg/ml, Dose-Norm C_{max} 0.878, T_{max} 6 h Group 3: 3 mg/kg, PND 35, AUC_{0-t} 9.27 mcg•hr/ml, Dose-Norm AUC_{0-t} 3.09, C_{max} 2.33 mcg/ml, Dose-Norm C_{max} 0.775, T_{max} 1 h Group 3: 12 mg/kg, PND 56, AUC_{0-t} 30.7 mcg•hr/ml, Dose-Norm AUC_{0-t} 2.56, C_{max} 6.13 mcg/ml, Dose-Norm C_{max} 0.510, T_{max} 1 h Group 4: 10 mg/kg, PND 7, AUC_{0-t} 167 mcg•hr/ml, Dose-Norm AUC_{0-t} 16.7, C_{max} 10.7 mcg/ml, Dose-Norm C_{max} 1.07, T_{max} 12 h Group 4: 10 mg/kg, PND 35, AUC_{0-t} 20.9 mcg•hr/ml, Dose-Norm AUC_{0-t} 2.09, C_{max} 3.21 mcg/ml, Dose-Norm C_{max} 0.321, T_{max} 2 h Group 4: 40 mg/kg, PND 56, AUC_{0-t} 95.6 mcg•hr/ml, Dose-Norm AUC_{0-t} 2.39, C_{max} 12.0 mcg/ml, Dose-Norm C_{max} 0.300, T_{max} 3 h **Table 3. Mean Plasma Values for TR-700 Toxicokinetic Parameters Female Sprague Dawley Rats on PNDs 7, 35, and 56.** Group 2: 1 mg/kg, PND 7, AUC_{0-t} 8.31 mcg•hr/ml, Dose-Norm AUC_{0-t} 8.31, C_{max} 0.697 mcg/ml, Dose-Norm C_{max} 0.697, T_{max} 1 h Group 2: 1 mg/kg, PND 35, AUC_{0-t} 7.58 mcg•hr/ml, Dose-Norm AUC_{0-t} 7.58, C_{max} 2.13 mcg/ml, Dose-Norm C_{max} 2.13, T_{max} 1 h Group 2: 2 mg/kg, PND 56, AUC_{0-t} 16.7 mcg•hr/ml, Dose-Norm AUC_{0-t} 8.37, C_{max} 2.98 mcg/ml, Dose-Norm C_{max} 2.98, T_{max} 1 h Group 3: 3 mg/kg, PND 7, AUC_{0-t} 39.1 mcg•hr/ml, Dose-Norm AUC_{0-t} 13.0, C_{max} 3.03 mcg/ml, Dose-Norm C_{max} 1.01, T_{max} 3 h Group 3: 3 mg/kg, PND 35, AUC_{0-t} 18.0 mcg•hr/ml, Dose-Norm AUC_{0-t} 5.99, C_{max} 3.28 mcg/ml, Dose-Norm C_{max} 1.09, T_{max} 2 h Group 3: 6 mg/kg, PND 56, AUC_{0-t} 44.6 mcg•hr/ml, Dose-Norm AUC_{0-t} 7.43, C_{max} 6.90 mcg/ml, Dose-Norm C_{max} 1.15, T_{max} 2 h Group 4: 10 mg/kg, PND 7, AUC_{0-t} 125 mcg•hr/ml, Dose-Norm AUC_{0-t} 12.5, C_{max} 9.69 mcg/ml, Dose-Norm C_{max} 0.969, T_{max} 3 h Group 4: 10 mg/kg, PND 35, AUC_{0-t} 53.3 mcg•hr/ml, Dose-Norm AUC_{0-t} 5.33, C_{max} 10.5 mcg/ml, Dose-Norm C_{max} 1.05, T_{max} 1 h Group 4: 20 mg/kg, PND 56, AUC_{0-t} 141 mcg•hr/ml, Dose-Norm AUC_{0-t} 7.04, C_{max} 22.9 mcg/ml, Dose-Norm C_{max} 1.14, T_{max} 1 h

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>50-Day, Oral Gavage, Toxicology Study with TR-701 FA in Juvenile Long Evans Rats/ Study No: TE.701.TX.003
Initial Doses for Males and Females (PND 7 to PND 42): 0 (vehicle), 1 mg/kg/day (Group); 3 mg/kg/day (Group 3); and 10 mg/kg/day (Group 4)
Developmental Doses for Males (PND 43 to PND 56): 0 (vehicle), 4 mg/kg/day (Group 2); 12 mg/kg/day (Group 3); and 40 mg/kg/day (Group 4)
Developmental Doses for Females (PND 43 to PND 56): 0 (vehicle), 2 mg/kg/day (Group 2); 6 mg/kg/day (Group 3); and 20 mg/kg/day (Group 4)</td><td>Sex differences: Three hours after dosing, plasma concentrations for TR-700 were 1.6- to 2.7-fold higher in females compared to males on PND 35 with increasing differences as the dose increased. Concentrations were similar between the sexes on PND 56 after the dose changes on PND 43 despite the doses being 2-fold lower in females.
Accumulation: Accumulation was difficult to assess because only TR-700 concentrations were measured and because the doses were changed on PND 43.
Dose proportionality: TR-700 concentration increases were slightly less than or dose proportional in plasma samples collected 3 hours after dosing in males and females on PND 35 and PND 56.

Table 4. Mean Plasma Concentrations of TR-700 in Male and Female Long Evans Rats Three Hours After Oral Administration of TR-701 FA on PNDs 35 and 56.
<table>
<tr><th>Group</th><th colspan="2">Dose (mg/kg/day)</th><th>PND</th><th colspan="2">Mean Concentration mcg/ml</th></tr>
<tr><th></th><th>Males</th><th>Females</th><th></th><th>Males</th><th>Females</th></tr>
<tr><td rowspan="2">Group 2</td><td>1</td><td>1</td><td>35</td><td>0.543</td><td>0.860</td></tr>
<tr><td>4</td><td>2</td><td>56</td><td>2.07</td><td>1.73</td></tr>
<tr><td rowspan="2">Group 3</td><td>3</td><td>3</td><td>35</td><td>1.47</td><td>2.78</td></tr>
<tr><td>12</td><td>6</td><td>56</td><td>5.27</td><td>6.45</td></tr>
<tr><td rowspan="2">Group 4</td><td>10</td><td>10</td><td>35</td><td>2.98</td><td>8.02</td></tr>
<tr><td>40</td><td>20</td><td>56</td><td>15.3</td><td>12.3</td></tr>
</table></td></tr>
</table>

Source: Table generated by the reviewer
Abbreviations: PND, postnatal day; AUC, Area under the plasma concentration time curve; C_{max}, maximal plasma concentration; T_{max}, time at which C_{max} occurs; Dose-Norm, Dose normalized; TR-701 FA, tedizolid phosphate; TR-700, tedizolid; ADME, Absorption, distribution, metabolism, and excretion; PK, pharmacokinetic

5.5. Toxicology

5.5.1. General Toxicology

The pivotal general toxicology studies conducted with TR-701 FA were reviewed in the 2014 Pharmacology/Toxicology Review for NDAs 205435 and 205436 by James Wild, PhD. The two juvenile toxicology studies conducted with oral TR-701 FA in rats are reviewed below.

Study title/ Number: TR-701 FA: A GLP 50-Day Oral (Gavage) Toxicity Study Including Toxicokinetics With a 28-Day Recovery Period in Neonatal Sprague-Dawley Rats./ TE.701.TX.002

- The mortality or moribundity of 6 high-dose males and 2 high-dose females was considered related to tedizolid phosphate (TR-701 FA) administration. Clinical signs observed in high-dose animals at about the time of weaning, from PND 18 to 26, included pale body and cool or pale extremities. In the prematurely deceased animals, clinical signs observed on the day of or the day before death, included partially closed eyes, increased and shallow respiration, prostration, hypoactivity, gasping, and dermal atonia.
- No ophthalmoscopy parameters or parameters assessed as part of the functional observational battery were changed in a TR-701 FA-related manner.
- Dose-normalized exposures to tedizolid (TR-700) were highest on PND 7 for high-dose animals with reductions in dose-normalized exposures on PND 35 before group dosages were increased on PND 43. The NOAEL for this study was considered to be the mid-dose of 3/12 mg/kg/day in males and 3/6 mg/kg/day in females with associated mean plasma AUC values of 38.3 mcg•hr/ml and 39.1 mcg•hr/ml respectively on PND 7.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	Oral gavage doses of TR-701 FA (Lot # 02120030, purity of 99.6%) were administered once per day. **Initial Doses for Males and Females (PND 7 to PND 42):** 0 (vehicle), 1 mg/kg/day (Group 2; low dose); 3 mg/kg/day (Group 3; mid dose) and 10 mg/kg/day (Group 4; high dose) **Developmental Doses for Males (PND 43 to PND 56):** 0 (vehicle), 4 mg/kg/day (Group 2; low dose); 12 mg/kg/day (Group 3; mid dose) and 40 mg/kg/day (Group 4; high dose)

	Developmental Doses for Females (PND 43 to PND 56): 0 (vehicle), 2 mg/kg/day (Group 2; low dose); 6 mg/kg/day (Group 3; mid dose) and 20 mg/kg/day (Group 4; high dose)
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) solution, pH 7.5, was used for formulation of the TR-701 FA dose solutions and as the vehicle in the vehicle control group.
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	30/sex/group divided as follows: Main Study (toxicity) animals: 10/sex/group; Recovery Study animals: 10/sex/group; and Fertility Study animals: 10/sex/group. Additional toxicokinetic animals included 18/sex/group.
Age:	At dosing initiation, rats were 7 days old (postnatal day 7)
Satellite groups/ unique design:	Satellite groups include the recovery, fertility, and toxicokinetic animals described above. Male and female Sprague Dawley rats were administered vehicle (b) (4) solution) or initial doses of 1, 3, and 10 mg/kg/day TR-701 FA on postnatal day 7 (PND 7). However, beginning on PND 43, dose levels were adjusted to 4, 12, and 40 mg/kg/day for males and 2, 6, and 20 mg/kg/day for females to offset an age- and sex-related decrease in exposure. Dosing with the new levels continued until PND 56 before the Main Study (toxicity) animals were euthanized and necropsied on PND 57. Recovery animals were maintained without additional dosing until PND 85 when they underwent necropsy. In addition, a fertility study was initiated on PND 57. In this study, male and female animals (10/sex/group) previously administered TR-701 FA from PND 7 to PND 56 were mated and assessed for fertility without additional dosing.
Deviation from study protocol affecting interpretation of results:	No

Table 5. Observations and Results: Changes From Control, Study No.: TE.701.TX.002

Parameters	Major findings
Mortality	The mortality or moribundity of 6 HD males and 2 HD females were considered related to TR-701 FA administration. In general, the clinical signs associated with TR-701 FA administration occurred during the weaning period from PND 11 to PND 26 in the HD group with improvement after weaning on PND 26. This pattern appears to have been influenced by TR-701 exposures which were highest on PND 7 with reductions in dose-normalized exposures on PND 35 before group dosages were increased on PND 43. For reasons not completely understood, plasma TR-701 exposures decreased as the juvenile animals aged.
Clinical Signs	Adverse clinical findings noted at the daily examinations or 1 to 2 hours after dose administration were observed in multiple male and female pups in the HD group, particularly those that died or were prematurely euthanized. Clinical sign in HD animals were most pronounced during the late preweaning period. Findings included pale body and cool or pale extremities from PND 18 to 26. Partial closure of the eyes, increased respiration, shallow respiration, prostration, hypoactivity, gasping, and dermal atonia were also noted for prematurely deceased HD males and females generally on the day prior to or on the day of death or euthanasia. No other clinical signs were considered related to TR-701 FA administration.
Body Weights	Significantly lower mean body weight gains were observed from PND 11 to 21 in HD males and females compared to the control group. Mean body weight gain for HD animals was generally similar to the control group from PND 21 through the remainder of the study and mean body weights were similar to the control group by PND 32 (males) or 33 (females). Mean body weights were decreased 16.7% and 16.8% compared to control values on PND 21 for HD males and females respectively. Mean body weights relative to control values were significantly reduced from PND 15 to 29 for HD males and PND 15 to 30 for HD females. Body weights and body weight gains in the LD and MD groups were similar to control values throughout dosing. Body weights for males and females in the TR-701-FA treatment groups were similar to control values during the recovery period.
Ophthalmoscopy	No TR-701-related ophthalmic findings were observed during the dosing or recovery periods.
Hematology	**PND 57:** Neutrophil counts and eosinophil counts were increased, sometimes to a statistically significant degree as shown below. However, the changes were not considered adverse. LD males: ↓35.5% neutrophil counts*

Parameters	Major findings
	MD males: ↓25.2% neutrophil counts MD females: ↓35.2% neutrophil counts* HD males: ↓38.1% neutrophil counts*; ↑86% eosinophil counts* HD females: ↓33.5% neutrophil counts **PND 85:** Mean values for hematology and coagulation parameters were similar in all groups.
Clinical Chemistry	No TR-701 FA-related effects on any serum chemistry parameters were noted at any dose level at the end of the dosing and recovery periods.
Urinalysis	No TR-701 FA-related alterations in urinalysis parameters were noted at any dose level at the end of the dosing and recovery periods.
Physical Development	**Balanopreputial Separation:** The mean ages of balanopreputial separation (ranging from 42.4 to 42.9 days after birth) and the mean body weights (ranging from 225.7 to 236.0 g) at the age of attainment were similar in the control and TR-701 FA-treatment groups. **Vaginal Patency:** The mean ages of vaginal patency (ranging from 33.4 to 33.8 days after birth) and the mean body weights at the age of attainment (ranging from 117.9 to 126.5 g) were similar in the control and TR-701 FA-treatment groups. **Functional Observation Battery:** No TR-701 FA-related changes were observed for the results of home cage observations, handling observations, open field observations, sensory observations, neuromuscular observations, physiological observations, motor activity, auditory startle response (dosing and recovery periods), and Biel Maze swimming trials (dosing and recovery periods).
Reproductive Performance	**Estrous Cycle:** The duration of estrous cycles were similar for all groups ranging from 4.1 to 4.2 days. **Fertility:** In the HD group, the mating index for males and females was 70% compared to 100% for male and female control values. This difference was not statistically significantly different, but the HD values were below the historical control range of 86.7 to 100%. The fertility index was also reduced to 60% for HD males and females compared to 90% in the control group. The 60% fertility index was not statistically significantly lower than the control value but was below the historical control range of 70.0% to 100.0%. The Applicant's explanation for the male and female mating and fertility index patterns is that the differences were primarily due to an absence of mating in three breeding pairs in the HD group and that the involved females were not observed to mate when subsequently paired with new males of proven fertility. These observations suggest a possible effect of TR-701 FA on female mating, but not male mating, with the reduced female mating potentially affecting male and female fertility rates. The Applicant

Parameters	Major findings
	reported that two of the three non-mating females in the HD group entered into persistent diestrus following initiation of breeding although the two rats exhibited a normal estrous cycle prior to the mating period. If results from the females with diestrus are excluded from the assessment, then the male and female mating and fertility indexes occur within the historical control range. Based on the available data, it seems likely that TR-701 FA did not substantially affect male mating or fertility. It is less clear that TR-701 FA did not in some way influence female mating behavior. However, the diestrus state of two HD females confounds interpretation of the data such that it is not clear that TR-701 FA affected female mating and fertility. **Spermatogenic Endpoint Evaluations:** In F0 generation male rats, no TR-701 FA-related effects that were considered toxicologically relevant were observed for any of the assessed spermatogenic endpoints (mean testicular and epididymal sperm numbers and sperm production rate, motility, and morphology). **Parturition (Fertility Phase):** No TR-701 FA-related effects on mean gestation length (mean values of 21.7 to 22.0 days for all groups) or the process of parturition were observed. **Pregnancy Parameters:** The mean number of implantation sites and corpora lutea were similar in the control and TR-701 FA treatment groups. **F1 Litter Data (Fertility Phase):** The mean number of pups born, live litter size, percentage of males per litter at birth, and postnatal survival in the intervals between birth and PND 0, PND 0 to 1, PND 1 to 4 (pre-culling), and birth to PND 4 were unaffected by administration of TR-701 FA to the F0 maternal animals at all dose levels. **F1 Clinical Signs:** The general physical condition (defined as the occurrence and severity of clinical findings) of all F1 pups in this study were unaffected by parental TR-701 FA administration. A total of 4, 1, 3, and 3 pups were found dead or euthanized in extremis in the control, LD, MD, and HD groups, respectively. A total of 3, 4, 3, and 2 pups in the same respective groups were missing and presumed to have been cannibalized. **F1 Body Weights:** Body weights were similar for pups in all groups on PNDs 1 and 4. **F1 Sex Determination:** At birth, the percent of male offspring in each group was 51.2, 48.2, 42.0, and 48.2% in the control, LD, MD, and HD groups respectively. The MD value was outside the historical control range of 44.2 to 57.3%, but since the reduction in percent males in this

Parameters	Major findings
	group did not occur in a dose-dependent manner, it was considered unlikely that the reduction in this group was TR-701 FA related. **F1 Gross Pathology:** The numbers of pups (litters) found dead or euthanized in extremis from PND 0 through euthanasia of the F1 generation (PND 4) were 4(3), 1(1), 3(2), and 3(1) in the control, LD, MD and HD groups, respectively. The three pups euthanized in extremis in the HD group all had a thin dermis with generalized white discoloration that was determined to be degloving and considered to be a malformation; however, all the affected HD pups were in a single litter consistent with the finding being a litter effect rather than TR-701 FA related.
Gross Pathology	In the primary phase and fertility phase animals, none of the gross observations were considered to be associated with administration of TR-701 FA at any dose level after the dosing and recovery periods. On Lactation Day 4 in the fertility phase in females that delivered, the mean numbers of implantation sites and corpora lutea were not changed in the TR-701 FA treatment groups compared to control values.
Organ Weights	At the primary necropsy at the end of dosing, mean kidney weights were significantly elevated in the HD males (relative to brain weight ↑13.4%) and females (relative to final body weight ↑10.5%) compared to control values. At the end of the recovery period, mean kidney weight in HD males remained elevated relative to brain weight (↑20%). No microscopic findings in the kidney correlated with the increased kidney weights. The increased kidney weights were considered related to TR-701 FA administration but not adverse.
Histopathology Adequate battery: Yes	No microscopic findings were considered related to TR-701 FA administration at the end of the dosing or recovery periods.

Parameters	Major findings
Bone Marrow Cytology	All stages of the erythroid and myeloid lineages were present with appropriate maturation sequence and predominance of mature precursors. A lower mean myeloid:erythroid ratio (M:E ratio) considered to be TR-701 FA related but not adverse was noted in HD males and females. The lower M:E ratios were a combination of a nonsignificant minimal increase in the proportion of erythroid cells and a significant minimal lowering of the proportion of myeloid cells. The lower proportion of myeloid cells was accompanied by minimally lower neutrophil counts in circulation. The TR-701 FA-related lower proportion of myeloid cells in HD males and females was due to minimally lower mean numbers of myeloblast (females), promyelocyte (males and females), and neutrophil precursors including myelocyte, metamyelocyte, band and segmented neutrophils (males and females).

Source: Table generated by the reviewer.
↓ indicates reduction in parameters compared to control.
* Statistically significantly different from control values.
Abbreviations: LD, low dose; MD, mid dose; HD, high dose; PND, postnatal day; TR-701 FA, tedizolid phosphate

Study Title/ Number: TR-701 FA: A GLP 50-Day Oral (Gavage) Toxicity Study With a 90-Day Recovery Period in Neonatal Long Evans Rats./ Study No.: TE.701.TX.003

- Five high-dose males and three high-dose females receiving an oral TR-701 FA dose of 10 mg/kg/day were found dead or euthanized in extremis from PND 21 to 28 during the dosing period, and the deaths were considered to be TR-701 FA related with concurrent clinical signs of pale body, blue abdomen, labored respiration and/or gasping in some animals.
- No ophthalmoscopy changes or parameters assessed as part of the functional observational battery were changed in a TR-701 FA-related manner.
- The NOAEL for this study was considered to be the mid-dose of 3/12 mg/kg/day in males and 3/6 mg/kg/day in females.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: Oral gavage doses of TR-701 FA (Lot # 02120030, purity of 99.6%) were administered once per day. **Initial Doses for Males and Females (PND 7 to PND 42):** 0 (vehicle), 1 mg/kg/day (Group 2; low dose); 3 mg/kg/day (Group 3; mid dose) and 10 mg/kg/day (Group 4; high dose)

	Developmental Doses for Males (PND 43 to PND 56): 0 (vehicle), 4 mg/kg/day (Group 2; low dose); 12 mg/kg/day (Group 3; mid dose) and 40 mg/kg/day (Group 4; high dose) **Developmental Doses for Females (PND 43 to PND 56):** 0 (vehicle), 2 mg/kg/day (Group 2; low dose); 6 mg/kg/day (Group 3; mid dose) and 20 mg/kg/day (Group 4; high dose)
Route of administration:	Oral gavage
Formulation/Vehicle:	The vehicle used for the formulation and administration of TR-701 FA was (b) (4)
Species/Strain:	Rat/ Long Evans
Number/Sex/Group:	10/sex/group for the dosing period animals; 10/sex/group for the recovery animals; and 2/sex/group for the toxicokinetic animals.
Age:	Dosing was initiated in 7-day old mice rats on postnatal day 7 (PND 7).
Satellite groups/ unique design:	Initial dose levels were 1, 3, and 10 mg/kg/day for males and females. However, beginning on PND 43, dose levels were adjusted to 4, 12, and 40 mg/kg/day for males and 2, 6, and 20 mg/kg/day for females to offset an age- and sex-related decrease in exposure. For this study, mortality, clinical signs, neurological assessments, ophthalmic assessments, toxicokinetics and brain histopathology were performed
Deviation from study protocol affecting interpretation of results:	No

Table 6. Observations and Results: Changes From Control, Study No.: TE.701.TX.003

Parameters	Major findings
Mortality	Five HD males and three HD females were found dead or euthanized in extremis during the dosing period from PND 21 to PND 28 (before and at weaning). The deaths were considered to be TR-701 FA related and overlapped in occurrence with observations of systemic toxicity in other HD animals including clinical signs (PND 17 to 33) and reductions in body weight (PND 12 to 23).

Parameters	Major findings
Clinical Signs	Clinical signs observed in the prematurely deceased animals included pale body and blue abdomen observed 1 to 2 hours following dose administration for several days prior to death or euthanasia as well as labored respiration, cool body, and/or gasping in some animals. In surviving HD males and females, clinical signs included pale body and blue abdomen 1 to 2 hours following dose administration. Pale body was noted for these animals as early as PND 17 and blue abdomen was noted as early as PND 22; both findings generally continued to be observed through PND 31 or 33. No TR-701 FA-related clinical findings were noted for LD and MD males and females.
Body Weights	Mean body weight gains were generally significantly lower for HD males and females from PND 12 or 13 to PND 23 compared to the control group. Mean body weight gains were similar to control values for HD animals after PND 23 for the remainder of the dosing period despite increased dose levels beginning on PND 43. Mean body weights were reduced up to 25.5% during PND 15 to 40 for HD males and 21.8% during PND 15 to 34 for HD females with significant reductions during the intervals of PND 15 to 33 and PND 15 to 34 for HD males and females respectively. Mean body weights were similar to the control group by PND 41 and PND 35 for HD males and females respectively. Mean body weight gains and body weights for males and females in the LD and MD groups were similar to control values during the dosing and recovery periods.
Ophthalmoscopy	No TR-701 FA-related ophthalmoscopy findings were observed near the end of the dosing and recovery periods.
Hematology	Not conducted
Clinical Chemistry	Not conducted
Gross Pathology	The prematurely deceased animals were not necropsied. None of the gross pathology findings in the surviving dosing or recovery animals were considered to be related to TR-701 FA administration.

Parameters	Major findings
Organ Weights (Only brain weights and sizes were evaluated)	No changes in brain weight or size were considered to be directly related to TR-701 FA administration at the primary or recovery necropsies on PNDs 57 and 147 respectively. Mean brain weights were non-significantly reduced for HD males (↓ 5.6%) and significantly reduced for HD females (↓ 6.5%) relative to control values. However, reduced brain weights at the end of the dosing period in the HD group correlated with general body weight reductions for HD males and females. The brain weight values in all groups were within the (b) (4) historical control range for rats 5-12 weeks of age and no histological findings were associated with the reduced brain weights. At the end of the recovery period, brain weights and sizes were similar in all groups.
Histopathology Adequate battery: A limited battery of primarily nervous tissues was examined including brain, spinal cord, skeletal muscle, eyes, optic nerves, sciatic nerves, and multiple spinal nerves in the cervical and lumber regions.	Degeneration of solitary nerve fibers were observed in several animals in the control and HD groups. Degeneration of solitary nerve fibers occurred in the trapezoid body of the medulla oblongata or in the ventral lumbar, peroneal, or tibial nerves. The degenerative fibers were recorded but consisted of isolated degenerations that were below the diagnostic threshold. The findings were not considered related to TR-701 FA because they occurred in control animals as well as HD animals and because axonal degeneration is reported to be commonly observed in all age groups of rats as an occasional spontaneous finding.
Other evaluations	No other evaluations were conducted.

Source: Table generated by the reviewer
Abbreviations: LD, low dose; MD, mid dose; HD, high dose; TR-701 FA, tedizolid phosphate; PND, postnatal day

5.5.2. Genetic Toxicology

The genetic toxicology studies conducted with TR-701 FA are reviewed in the 2014 Pharmacology/Toxicology Review for NDAs 205435 and 205436 by James Wild, PhD.

5.5.3. Reproductive and Developmental Toxicology

The developmental and reproductive toxicology studies conducted with TR-701 FA are reviewed in the 2014 Pharmacology/Toxicology Review for NDAs 205435 and 205436 by James Wild, PhD.

6. Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology (OCP) reviewed the information submitted in these sNDAs. The clinical pharmacology information submitted supports the approval of SIVEXTRO (tedizolid phosphate) for the treatment of ABSSSI caused by designated susceptible bacteria in pediatric patients from (b) (4) (at least 26 weeks gestational age) and older with a weight ≥1 kg. See Table 7 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 7. Summary of OCP Recommendations and Comments on Key Review Issue

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness and safety	**Effectiveness:** The effectiveness of the Applicant's final proposed (hereon/hereafter referred as the proposed) tedizolid phosphate dosage for pediatric ABSSSI patients (Table 9) is principally supported based on the extrapolation of effectiveness from the approved tedizolid phosphate dosage for adult ABSSSI patients. The proposed pediatric tedizolid phosphate dosage based on weight-bands was not evaluated in clinical trials, except for pediatric subjects weighing 1 to <2 kg. However, the Applicant has provided pharmacokinetic (PK) simulation findings from a population PK (popPK) model in support of the effectiveness and safety of the proposed dosage. Specifically, the effectiveness extrapolation is based on the combined findings of the following clinical pharmacology aspects: • Tedizolid exposure comparisons for the proposed dosage between pediatric and adult ABSSSI patients showed that following the Applicant's proposed pediatric tedizolid phosphate dosage: ○ Tedizolid exposures as mean area under the concentration-time curve over 24 hours (AUC_{0-24}) in pediatric patients were generally comparable to the adult AUC_{0-24} reported following the currently approved adult tedizolid phosphate dosage. ○ Tedizolid exposures as maximum concentration (C_{max}) in pediatric patients were comparable to or lower than the adult C_{max} reported following the currently approved adult tedizolid phosphate dosage.

Additional supportive evidence is from the following:

- The clinical response data in pediatric patients with ABSSSI that were obtained from two phase 3 pediatric safety, efficacy, and PK trials (i.e., trials MK-1986-012 and MK-1986-018) that evaluated tedizolid phosphate for the proposed indication in a pediatric population (See Section 8.1 for review of MK-1986-018). Study MK-1986-012 was reviewed previously as part of supplements 12 and 7 for NDAs 205435 and 205436, respectively, see NDA Multi-disciplinary Review (DARRTS date 06/18/2020) for NDAs 205435/S-012 and 205436/S-007 for details.
- The probability of pharmacokinetic pharmacodynamic target attainment (PTA) for tedizolid phosphate in pediatric ABSSSI patients were comparable to the tedizolid phosphate PTA findings in adults. PTA assessments also showed that with the Applicant's proposed pediatric tedizolid phosphate dosage, PTA estimates in pediatric ABSSSI patients were above 90%, approaching 100%, for the tedizolid susceptibility breakpoint of minimum inhibitory concentration (MIC) of 0.5 µg/mL for *Staphylococcus aureus,* which is the same as the susceptibility breakpoint the Applicant proposed for adult ABSSSI patients in the original NDA filing. See Section 17.4.3 for additional details on PTA analysis findings.

Safety:
The evidence of safety is based on the safety and tolerability findings from three phase 1 trials (MK-1986-013, MK-1986-014, and MK-1986-026) and two phase 3 trials (MK-1986-012 and MK-1986-018) that enrolled pediatrics, as shown in Table 8 below. The approved adult dosage of 200 mg tedizolid phosphate once daily administered by IV, as an oral tablet, or an oral suspension, was well tolerated in pediatric subjects with body weights ranging from 27.6 to 126.3 kg. Twice daily tedizolid phosphate was well tolerated up to dosage of 3 mg/kg administered by IV or as an oral suspension (Table 8). See Section 10 for the evaluation of safety findings.

Further evidence of safety is from the comparison of the simulated exposures for the proposed dosage from the popPK model in the pediatric population with the adult and adolescent exposures reported following the currently approved adult and adolescent tedizolid phosphate dosage.

Review Issue	Recommendations and Comments

Table 8. Summary of Studies Supporting Safety and Tolerability of Tedizolid Phosphate in Pediatric Patients

Study (number, n)	Age Range (years, inclusive)	Weight Range (kg)	Tedizolid Phosphate Dosage Range
MK-1986-012 (n=120)	12 to 18	27.6 to 126.3	200 mg once-daily for at least 6 days
MK-1986-026 (n=20)	11 to 17	38.5 to 83.1	200 mg single dose
MK-1986-013 (n=32)	2 to 11	12.6 to 42.3	3 to 6 mg/kg, single dose
MK-1986-014 (n=47)	0.0027 to 1.7	1.05 to 14	2.5 to 3 mg/kg, single dose (n=39) or multiple dose twice daily for 3 days (n=8)
MK-1986-018 (n=75)	0.33 to 11	6 to 59	2 to 2.5 mg/kg twice daily, or 200 mg once-daily if body weight ≥50 kg for at least 6 days

Source: Reviewer compiled

See Section 6.2.1 for the detailed findings on the exposure comparison. See Section 10.2 for the evaluation of safety findings.

General dosing instructions

The recommended dosage for both of the commercially available SIVEXTRO (tedizolid phosphate) for injection, for intravenous use and SIVEXTRO (tedizolid phosphate) tablet, for oral use are as follows:

SIVEXTRO (tedizolid phosphate) for IV infusion:
The table below shows the recommended IV dosage of tedizolid phosphate in pediatric patients from (b) (4) (i.e., full-term and pre-term neonates with gestational age ≥26 weeks and weight ≥1 kg) to <18 years of age. All IV doses are to be administered as a 1 hour infusion with a recommended treatment duration of 6 days.

Table 9. Recommended Intravenous Dosage of SIVEXTRO for Injection for Pediatric Patients With ABSSSI

Weight-band (kg)	Dose	Frequency	Infusion time	Duration
Pediatric Patients Weighing Less than 2 kg*				
1 to <2	3 mg/kg	Twice daily	1 hour	6 days

Review Issue	Recommendations and Comments

Pediatric Patients Weighing at Least 2 kg				
2 to <3	6 mg	Twice daily	1 hour	6 days
3 to <6	12 mg			
6 to <10	20 mg			
10 to < 14	30 mg			
14 to <20	40 mg			
20 to <35	60 mg			
Pediatric Patients Weighing at Least 35 kg				
≥ 35	200 mg	Once daily	1 hour	6 days

Source: Reviewer compiled from Applicant's annotated draft labelling text and clinical information amendment submitted on February 11, 2025.
*Recommended Dosage for 1 kg to less than 2 kg is based on actual body weight.

SIVEXTRO (tedizolid phosphate) oral tablet:
The recommended oral dosage of tedizolid phosphate in pediatric patients with a weight greater than 35 kg, irrespective of age, is a 200 mg SIVEXTRO oral tablet once daily with a recommended treatment duration of 6 days. The currently available oral tablet formulation strength does not allow derivation of dosage recommendation for pediatric patients with weight less than 35 kg.

Table 10. Recommended Oral Tablet Dosage of SIVEXTRO for Pediatric Patients With ABSSSI

Weight-band (kg)	Dose	Frequency	Duration
≥ 35	200 mg	Once daily	6 days

Source: Reviewer compiled from Applicant's annotated draft labelling text.

Dosing in patient subgroups (intrinsic and extrinsic factors)	For pediatric patients, no dosage individualization is recommended based on intrinsic or extrinsic factors. No new clinical pharmacology information on intrinsic or extrinsic factors was submitted in these sNDAs that suggest the need for dosage individualization. The popPK model that describes the pediatric tedizolid PK is dependent on the subject's actual body weight for the structural model estimation of clearance and volume parameters. No other covariates were found to have a significant effect on tedizolid PK in a popPK covariate analysis. Therefore, only a patient's actual body weight is considered for the recommended dosage.
Labeling	The Applicant's proposed labeling was reviewed, and the review team conveyed specific recommendations to the Applicant. See Labeling Recommendations in Section 13 for additional details.

Source: Reviewer compiled.
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections

6.2. Comprehensive Clinical Pharmacology Review

6.2.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness and safety?

Yes, the clinical pharmacology program provides evidence of effectiveness for the Applicant's proposed tedizolid phosphate dosage for pediatric ABSSSI patients from (b) (4) (i.e., full-term and pre-term neonates with gestational age ≥26 weeks and weight ≥1 kg) to <18 years of age. Specifically, the clinical pharmacology program provides tedizolid exposure comparison findings between pediatric and adult ABSSSI patients who primarily supports the effectiveness of Applicant's proposed pediatric tedizolid phosphate dosage. The PTA findings for tedizolid phosphate in pediatric ABSSSI patients further provide supportive evidence of effectiveness.

Clinical Pharmacology Program

Tedizolid is the active moiety of the prodrug tedizolid phosphate. Tedizolid phosphate is rapidly metabolized to the active moiety tedizolid by endogenous plasma and tissue phosphatases in vivo. Tedizolid is metabolized by multiple sulfotransferase enzymes in vivo to an inactive and noncirculating sulphate conjugate found in feces. Tedizolid is substantially excreted in the feces as the inactive sulphate conjugate. Both phosphatase and sulfotransferase metabolizing enzymes are present and fully functional at birth. Therefore, the popPK model utilized to characterize and simulate tedizolid PK included clearance and volume parameters that were scaled using an allometric relationship (using estimated exponents) without any ontogeny parameters. The popPK model utilized PK data from multiple clinical trials as summarized below.

The clinical pharmacology program is comprised of: (1) study MK-1986-018, a phase 3, randomized, active-comparator, parallel-group, multisite, assessor-blinded study to assess the PK, safety, and efficacy of tedizolid phosphate for the treatment of ABSSSI in pediatric subjects aged 28 days to <12 years of age; (2) study MK-1986-012, a phase 3, randomized, active-comparator, multisite, parallel-group, assessor-blinded study to assess the PK, safety, and efficacy of tedizolid phosphate for the treatment of ABSSSI in pediatric subjects aged 12 to <18 years of age; (3) study MK-1986-014, a phase 1, PK, safety, and tolerability study in pediatric subjects aged 2 to <12 years receiving prophylaxis for or with a confirmed or suspected infection with gram-positive bacteria study; (4) tedizolid-phosphate popPK analyses; and (5) tedizolid-phosphate PTA analysis.

Exposure Comparison for Evidence of Effectiveness

The PopPK analyses demonstrate that the simulated steady state tedizolid exposures resulting from the proposed dosage in pediatric patients are reasonably similar to the efficacious exposures in adults receiving the currently approved tedizolid oral dosage for the same indication. These findings support the effectiveness extrapolation from adults to pediatrics based on expectation that ABSSSI is pathophysiologically similar in adults and pediatric patients

and, therefore, the efficacious tedizolid exposures in adults are also expected to be effective across the entire pediatric population.

Additional Supportive Evidence of Effectiveness
Blinded investigator assessment of the clinical response was determined as a secondary outcome of phase 3 study MK-1986-018 in pediatric patients aged 28 days to <12 years of age. While this outcome was not powered for an efficacy analysis, greater than 90% clinical success at end of treatment (EOT) and test of cure (TOC) visit (22 to 29 days after first dose) were observed for the tedizolid phosphate arm, which was generally comparable to the comparator arm (see Table 21).

PTA results for tedizolid phosphate demonstrated that pharmacokinetic/pharmacodynamic (PK/PD) target attainment rates are comparable between (A) adults receiving the currently approved tedizolid phosphate dosage for the same indication and (B) the proposed pediatric population receiving the Applicant's proposed tedizolid phosphate dosage in this submission. PTA assessments also showed that with the Applicant's proposed pediatric tedizolid phosphate dosage, PTA estimates in pediatric ABSSSI patients were above 90%, approaching 100%, for the tedizolid susceptibility breakpoint of minimum inhibitory concentration (MIC) of 0.5 µg/mL for *Staphylococcus aureus*, which is same as the susceptibility breakpoint the Applicant proposed for adult ABSSSI patients in the original NDA filing. (See Section 17.4.3.2.3 for additional details).

Exposure Comparison for Safety
Of note, the proposed pediatric weight-band tedizolid phosphate dosage (Table 9 and Table 10) was not evaluated in pediatric clinical trials; however, the proposed dosage is supported based upon simulated tedizolid exposures from the popPK model. Specifically, the proposed pediatric IV weight-band based tedizolid phosphate dosage is equivalent to a weight-band dosage range of 1.7 to 4 mg/kg. From a safety perspective, the proposed dosage is supported by safety data for (A) 2 to 6 mg/kg tedizolid phosphate administered to pediatric subjects in study MK-1986-013, (B) 2.5 to 3 mg/kg tedizolid phosphate administered to pediatric subjects in study MK-1986-014, and (C) 2 to 2.5 mg/kg tedizolid phosphate administered to pediatric subjects in study MK-1986-018. In addition, the safety of proposed IV dosage of 3 mg/kg tedizolid phosphate twice daily for pediatric patients with ABSSSI weighing 1 to <2 kg, both preterm and full term neonates with gestational age ≥26 weeks, was evaluated in Phase 1 clinical study MK-1986-014.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?
Primarily based on the findings related to tedizolid exposure comparison between pediatric and adult patients (summarized above and in Table 13 and Figure 1), the Applicant's initially proposed tedizolid phosphate dosages for IV and oral administration (Table 11 and Table 12) in patients from birth to <18 years of age are acceptable for all weight bands except (b) (4)

(b) (4) The evaluation of the Applicant's initially proposed tedizolid phosphate IV dosage for patients weighing (b) (4) is summarized below. See Section 17.4.3.2.2 for additional details.

(b) (4)

Table 11. Applicant's Initial Proposed Weight-Band Intravenous Dosage of SIVEXTRO for Pediatric Patients With ABSSSI

Weight band (kg)	Dose	Frequency	Infusion time	Duration
(b) (4)		Twice daily	1 hour	6 days
3 to <6	12 mg			
6 to <10	20 mg			
10 to < 14	30 mg			
14 to <20	40 mg			
20 to <35	60 mg			
≥ 35	200 mg	Once daily		

Source: Reviewer compiled from Applicant's annotated draft labelling text.
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections

Table 12. Applicant's Initial Proposed Oral Tablet Dosage of SIVEXTRO for Pediatric Patients With ABSSSI

Weight band (kg)	Dose	Frequency	Duration
≥ 35	200 mg	Once daily	6 days

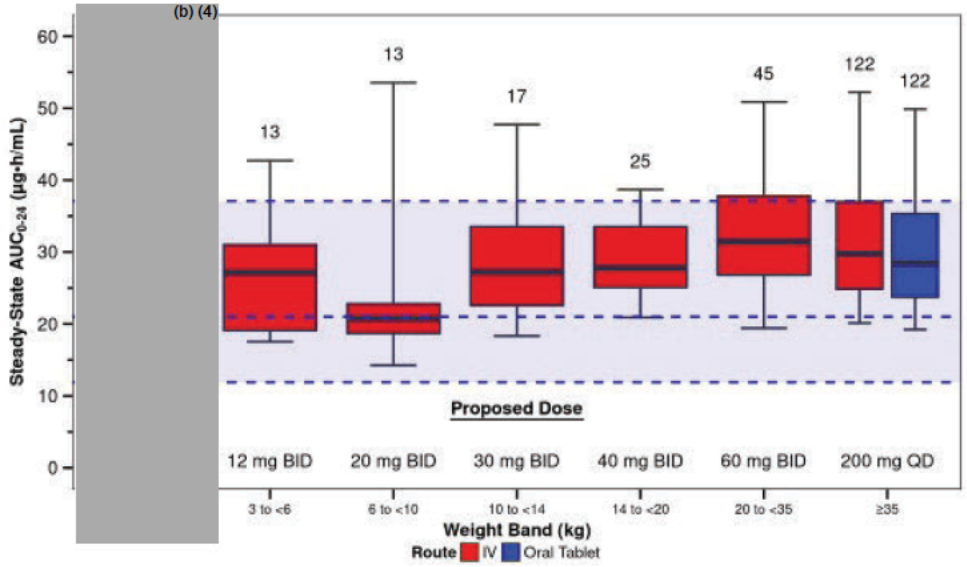
Source: Reviewer compiled from Applicant's annotated draft labelling text.
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections

Table 13. Geometric Mean (%CV) of Steady-State Tedizolid Exposures for Proposed SIVEXTRO IV and Oral Tablet Dosage Simulated in Actual Pediatric Subjects , by Weight-Band Group, Compared to Adults and Adolescents From the Phase 2/3 Studies

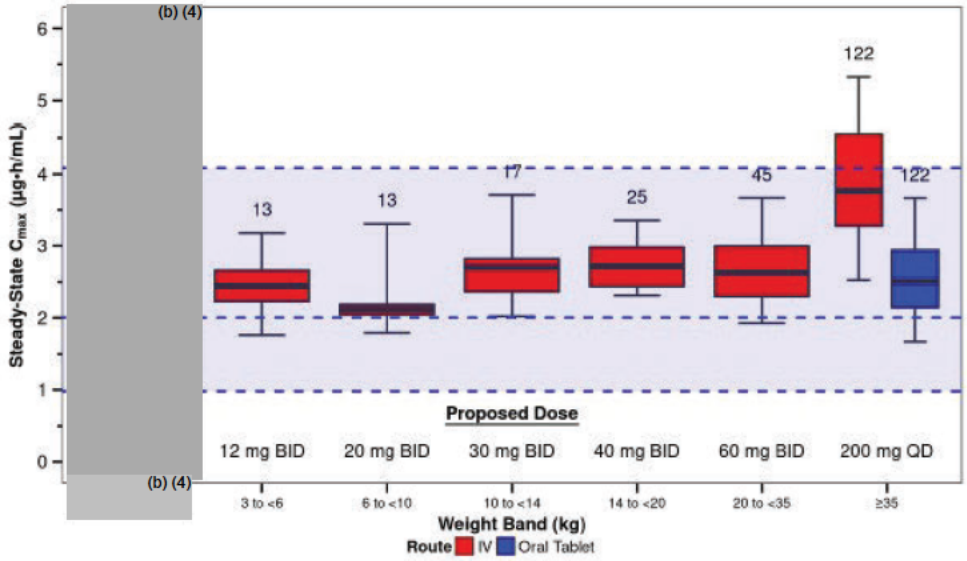
Population	Age (years)	Product	Weight Band (kg)	Dose (mg)	Frequency	N	AUC_{0-24} (µg*h/mL)	C_{max} (µg/mL)
Pediatric [a]	<18	IV	(b) (4)					
			3 to <6	12	BID	13	26.40 (34.38)	2.40 (20.71)
			6 to <10	20	BID	13	22.54 (43.87)	2.22 (20.37)
			10 to <14	30	BID	17	27.61 (32.14)	2.68 (19.57)
			14 to <20	40	BID	25	28.44 (22.09)	2.74 (12.95)
			20 to <35	60	BID	45	31.40 (29.94)	2.61 (21.63)
			≥35	200	QD	122	30.63 (29.68)	3.83 (23.90)
		Oral tablet	≥35	200	QD	122	29.25 (29.67)	2.50 (24.42)
(b) (4)								
Adult[c]	>18	tablet	-	200	QD	830	28.6 (26.6, 30.8)[d]	3.13 (2.89, 3.38)[d]

Source: Reviewer compiled from Table 37 (adolescent), and 48 (pediatric and adult) popPK report.
[a] Simulated tedizolid exposures for actual pediatric subjects aged birth to <18 years from studies MK-1986-013, MK-1986-014, MK-1986-018, MK-1986-012, and MK-1986-026 administered proposed SIVEXTRO pediatric dosage corresponding to the patient's actual body weight.
[b] Adolescent data from Study MK-1986-012, estimated by pediatric popPK model.
[c] (Li D et al. 2021)
[d] Summary statistics reported in adults are geometric mean and 95% confidence interval.
Abbreviations: BID, twice daily; CV, Coefficient of Variation; IV, intravenous; QD, once daily

Figure 1. Comparison of Simulated Steady-State Tedizolid AUC_{0-24} and C_{max} Based Upon Administration of Proposed Weight-Banded Dosage Regimen for Intravenous and Oral Tablet Tedizolid Phosphate in Pediatric Subjects (Birth to < 18 Years) From the Population Pharmacokinetic Analysis Population, Versus Adult (Phase 3) Studies



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. The number of participants is above each box. Horizontal blue dashed lines represent the adult geometric mean and 5th/95th percentiles.



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. The number of participants is above each box. Horizontal blue dashed lines represent the adult geometric mean and 5th/95th percentiles.

Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; BID, twice daily; C_{max}, maximum plasma concentration; IV, intravenous; QD, once daily.

Source: Adapted using an excerpt of Figure 52 popPK report.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 14. Listing of Clinical Trials Relevant to This NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of subjects enrolled	Study Population	Center/ Country
Controlled Studies to Support Safety and Efficacy								
MK-1986-018	03176134	Randomized, investigator blinded, multicenter study	Tedizolid phosphate IV/PO tedizolid weight based:* 3.2 kg to <30 kg: 2.5 mg/kg BID 30 kg to <50 kg: 2 mg/kg BID ≥50 kg: 200 mg daily Comparators: vancomycin, linezolid, clindamycin, flucloxacillin, cefazolin (administered IV) and/or linezolid,	Primary objective was to compare safety between tedizolid and comparator	Tedizolid phosphate: x6 to 10 days Comparator: x10 to 14 days	Total: 100 Tedizolid: 75 Comparator: 25	Pediatric subjects birth to <12 years	20 centers in 10 countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of subjects enrolled	Study Population	Center/ Country
			clindamycin, flucloxacillin, cephalexin (administered orally)					
		Studies to Support Safety						
MK-1986-014	00983255	Non-randomized, open-label, multicenter pharmacokinetic and safety study	First 5 participants aged 28 days to <6 months: Tedizolid: 3.0 mg/kg IV All other participants: Tedizolid <10 kg: 3.0 mg/kg IV/PO* 10 kg to <30 kg: 2.5 mg/kg IV/PO*	Primary objective was to assess single-dose PK of IV and oral and multiple-dose PK of IV tedizolid phosphate. Secondary objective was to evaluate the safety and tolerability of single-dose oral and IV and multiple-dose IV tedizolid phosphate.	Multiple IV infusions administered to 4 preterm neonates (birth to <28 days) and 4 term neonates (birth to <28 days) BID x3 days. All others received single dose IV or oral	Total: 47 28 days to ≤2 years (N=14); Term neonates birth to ≤28 days: (N=16); Pre-term neonates (GA ≥26 weeks) birth to ≤28 days: (N=17)	Pediatric subjects birth to <2 years of age	18 centers in 5 countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of subjects enrolled	Study Population	Center/ Country
MK-1986-013	02750761	Non-randomized, open-label, multicenter, pharmacokinetic and safety study	Tedizolid IV 6 to <12 years: 4 mg/kg or 5 mg/kg 2 to <6 years: 3 mg/kg or 6 mg/kg Tedizolid PO* 6 to 12 years: 4 mg/kg 2 to <6 years: 3 mg/kg	Primary objective was to assess the single dose PK of IV tedizolid phosphate and the bioavailability of tedizolid after single oral dose. Secondary objective was to evaluate the safety and tolerability of IV and oral dose of tedizolid.	Single dose IV/PO	Total: 32 2 to <6 years: 16 6 to <12 years: 16	Pediatric subjects aged 2 to <12 years	15 centers in 4 countries	

Source: Created by Clinical Reviewer
*: For PO dosing, oral suspension was used
Abbreviations: BID, twice a day; IV, intravenous; PO, oral; pk, pharmacokinetic; GA, gestational age

7.2. Review Strategy

The review focuses on Study MK-1986-018, "A Phase 3 Randomized, Active-comparator-controlled Clinical Trial to Study the Safety and Efficacy of MK-1986 (Tedizolid Phosphate) and Comparator in Subjects from Birth to less than 12 Years of Age with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)." In addition to the phase 3 study, two phase 1 studies were also submitted to supplement the safety data. One study enrolled 47 pediatric subjects less than 2 years of age, and the other study enrolled subjects from 2 to <12 years of age. These studies, submitted with the sNDA, provided additional evidence of safety in pediatric patients aged less than 12 years. The efficacy of SIVEXTRO in pediatric patients is primarily based on extrapolation from findings in adult patients by matching tedizolid phosphate exposures in pediatric patients to exposures in adults.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials

8.1.1. Study MK-1986-018

Trial Design

Study MK-1986-018 (hereafter referred to as Study 018, clinicaltrials.gov identifier NCT03176134) was a phase 3, randomized, assessor blinded, active-controlled, multicenter, parallel group trial. Its objectives were to evaluate the safety and efficacy of IV and oral tedizolid phosphate versus the comparator therapy in pediatric subjects <12 years of age with ABSSSI requiring antibacterial therapy and caused by suspected or documented gram-positive pathogens. Allowed comparators per local standard of care were selected as follows:

- Allowed IV comparators: vancomycin, linezolid (outside the European Union [EU] only, as not approved for pediatric use in the EU), clindamycin, flucloxacillin, and cephazolin (cefazolin);
- Allowed oral comparators: linezolid (outside the EU only, as not approved for pediatric use in the EU), clindamycin, flucloxacillin, and cephalexin (cefalexin).

Choice of comparator was not to be switched during the study, unless an IV-to-oral switch was warranted, and no oral formulation was available for the selected IV comparator.

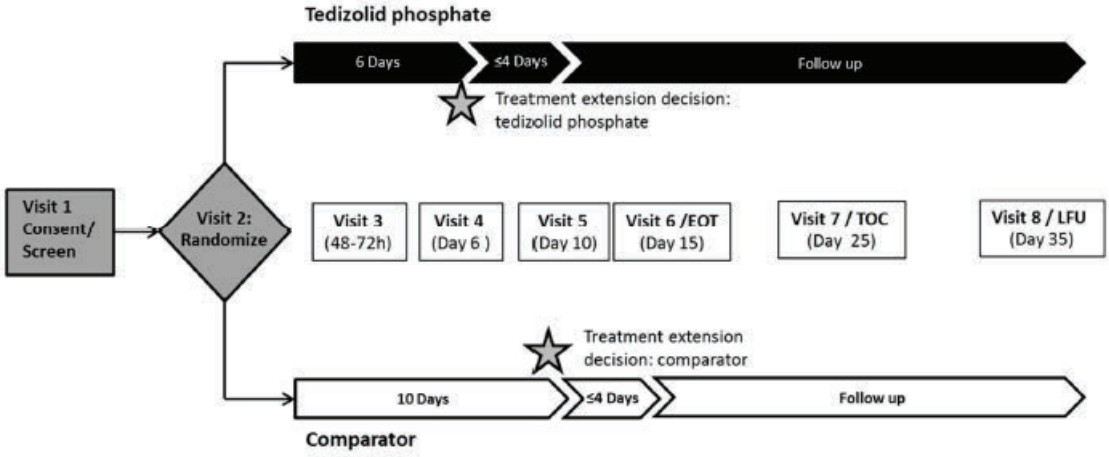
Study 018 randomized 100 subjects in a 3:1 ratio to receive tedizolid IV and/or oral therapy, dosed 200 mg once daily for 6 days (75 patients), or comparator IV and/or oral therapy, dosed over 10 days (25 patients). Subjects were stratified and enrolled by age into 1 of 4 cohorts:

- Cohort 1: 6 to <12 years of age;
- Cohort 2: 2 to <6 years of age;
- Cohort 3: 28 days to <2 years of age; or
- Cohort 4: birth to <28 days of age (term and preterm neonates with gestational age of at least 26 weeks at birth)

As of database lock, there were 44 subjects in Cohort 1, 16 subjects in Cohort 2 and 15 subjects in Cohort 3 who received tedizolid. There were no subjects enrolled in Cohort 4.

Each subject participated in the trial for up to 41 days from the time their legally acceptable representative provided documented informed consent through the final contact. As shown in Figure 2, each subject received assigned treatment for 6-14 days, depending on treatment assignment and whether the subject received a treatment extension of up to 4 days. After the end of treatment, each subject was followed through Study Day 35.

Figure 2. Study Schema, Study 018



EOT=End of Therapy; LFU=Late Follow-up; TOC=Test-of-Cure.

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

Source: Study 018 Clinical Study Report (CSR) - Figure 9-1

Inclusion/Exclusion Criteria:

Eligible subjects were male or female, aged birth to <12 years (preterm neonates were to have a gestational age of ≥26 weeks at birth). Additional criteria included:

- Have ABSSSI requiring antibacterial drug therapy, defined by meeting the definition of at least 1 of the following 3 clinical syndromes.
    - Cellulitis/erysipelas defined as a diffuse skin infection.
    - Major cutaneous abscess, defined as an infection characterized by a collection of pus apparent upon visual examination within the dermis or deeper.
    - Wound infection, defined as an infection characterized by purulent drainage from a wound with surrounding erythema, edema, and/or induration.
- Have local symptoms of ABSSSI that started within 14 days before Study Day -1.
- Have a suspected or documented gram-positive infection from baseline Gram stain or culture.
- Have body weight ≥3.2 kg for children aged 28 days to <12 years.

Exclusion criteria included:

- Has an uncomplicated skin and skin structure infection. Has ABSSSI due to or associated with any of the conditions defined in the protocol, including suspected or documented gram-negative pathogens in subjects with cellulitis/erysipelas or major cutaneous abscess
- Has known bacteremia, severe sepsis, or septic shock at the Screening visit
- Has significant or life-threatening condition, disease, or organ system condition
- Has received at least 48 hours of effective antibacterial therapy for treatment of the current episode of ABSSSI.

Study Endpoints

Primary Endpoint- The primary endpoint was the overall safety assessment of tedizolid phosphate evaluated in the All Participants as Treated (APaT) population. Multiple assessments were conducted to evaluate the safety:

- Adverse events (AEs);
- Vital signs;
- Physical exams including specific neurological and visual acuity assessments;
- Hematology and clinical chemistry.

Key Secondary Endpoint- The key secondary endpoint was 'Clinical Response at the Test of Cure Visit.' This endpoint occurred on Day 18-25 and was assessed by a blinded investigator in the ITT and CE-TOC populations (defined below in the 'Section 8.1.1.1).

As shown in Table 15, a 'Clinical Success' was required to have resolution or near resolution of all related signs and symptoms such that no further antibacterial therapy was needed.

Table 15. Investigator's Assessment of Clinical Response Definitions (EOT and TOC Visits), Study 018

Term	Definition
Clinical Success	All of the following: • Resolution or near resolution of most disease-specific signs and symptoms • Absence or near resolution of regional or systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal white blood cell count), if present at baseline • No new signs, symptoms, or complications attributable to the infection under study
Clinical Failure	Any of the following: • Requires additional antibiotic therapy for treatment of the primary lesion • Unplanned major surgical intervention required due to failure of study drug (i.e., amputation) • Developed osteomyelitis after baseline • Persistent gram-positive pathogen bacteremia • TEAE leading to discontinuation of study drug and subject required additional antibiotic therapy to treat the infection under study • Death (all-cause mortality) within 28 days of first infusion
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Osteomyelitis present at baseline • Subject lost to follow-up • Extenuating circumstances that preclude the classification of a clinical success or failure • For subjects with cellulitis/erysipelas or major cutaneous abscess: Gram-negative organism isolated at baseline that required a different antibiotic therapy • For subjects with wound infections: Gram-negative organism isolated at baseline that required a different antibiotic therapy other than aztreonam or metronidazole • Subject withdraws consent

Source: Study 018 Protocol - Table 4
Abbreviations: EOT, end of treatment; TOC, test of cure; TEAE, treatment-emergent adverse event

Other Secondary Endpoints- Another secondary efficacy endpoint of interest was 'Early Clinical Response', which was assessed in the ITT population. Patients were assessed at 48-72 hours after start of treatment as either a 'Responder' (≥ 20% reduction from baseline lesion area), a 'Nonresponder' (<20% reduction from baseline lesion area), or as 'Indeterminate' (lesion area data missing).

Additional efficacy endpoints included assessment of palatability, rate of relapse, superinfection and new infection.

Clinical relapse was assessed as follows at the Late Follow-up Visit, as shown in Table 16.

Table 16. Investigator's Assessment of Clinical Relapse Definitions (Late Follow-up Visit), Study 018

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

Source: Study 018 Protocol – Table 6
Abbreviations: ABSSSI, Acute Bacterial Skin and Skin Structure Infections; TOC, test of cure

Microbiological Endpoints

Additional efficacy endpoints included Microbiological Response at TOC Visit on Day 25 (microbiological intent-to-treat (MITT) and microbiological evaluable (ME) Populations). Microbiological response definitions for this endpoint are shown in Table 17.

Table 17. Microbiological Response Definitions, Study 018

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

Source: Study 018 Protocol (Version 7.0), Table 11
Abbreviations: ABSSSI, Acute Bacterial Skin and Skin Structure Infections

8.1.1.1. Statistical Analysis Plan

Analysis Populations

The following analysis populations were defined:

Intent-to-Treat (ITT)- all randomized subjects

CE-TOC-ITT subjects meeting the following criteria:

- Have a confirmed ABSSSI clinical diagnosis;
- Have a suspected or documented gram-positive infection from baseline Gram stain or
- culture;
- Met all other inclusion criteria and met no exclusion criteria;
- Have received a sufficient course of therapy:
    - Received at least 48 hours of dosing with study drug and the correct study drug based on the randomization assignment
- Completed EOT, and TOC investigator's assessments (unless assessed as failures at any time point before the TOC Visit)
- Had no concomitant systemic antibiotic therapy from first infusion of study drug through TOC Visit that is potentially effective against baseline pathogen except adjunctive AZ and/or MNZ in subjects with wound infections.

MITT -**ITT** subjects with at least one gram-positive pathogen at baseline

ME-**MITT** subjects who are also in the CE-TOC population

APaT- All ITT subjects receiving at least one dose of treatment

Statistical Methods for Efficacy
No hypothesis testing was planned. The number and percentage of subjects with an investigator's assessment of clinical success, clinical failure, and indeterminate response at TOC in the ITT and CE-TOC populations were summarized for each treatment group. The difference between treatment groups in the rate of clinical success was estimated along with a two-sided 95% CI for the treatment difference using the method of Miettinen and Nurminen stratified by age cohort.

Interim Analyses
Study 018 employed a data monitoring committee (DMC) which had planned DMC reviews after the first 5 tedizolid-treated subjects in each cohort were enrolled, and additionally at 33% and 66% of the total enrollment. The DMC reviewed accruing data including safety and efficacy during the course of the study. There were no formal stopping criteria for efficacy or safety.

Sample Size and Power
The planned sample size in Study 018 was approximately 100 subjects. This ensured that at least 75 subjects received tedizolid phosphate and were evaluable for safety; subjects not evaluable for safety were replaced. With an estimated drop-off rate of 5%, 95 subjects were expected to receive study treatment. With 72 subjects receiving tedizolid phosphate, the probability of detecting at least one serious adverse event (SAE) with a true underlying incidence rate of 2% was 77%.

Protocol Amendments

The initial protocol for this study was issued in July 2016 and this was followed by 7 general amendments with Version 7 of the final protocol issued in June 2022. Key changes in Version 7 of the protocol (compared to Version 6 **issued in May 2021) included the following:**

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

It is also noted that part of this study was conducted during the COVID-19 pandemic. However, no contingency methods were enacted except for reducing some requirements for in-person visits to allow telephone interviews.

8.1.2. Study Results

Compliance With Good Clinical Practices

This trial was conducted in conformance with Good Clinical Practice and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (International Council for Harmonisation)) guidelines.

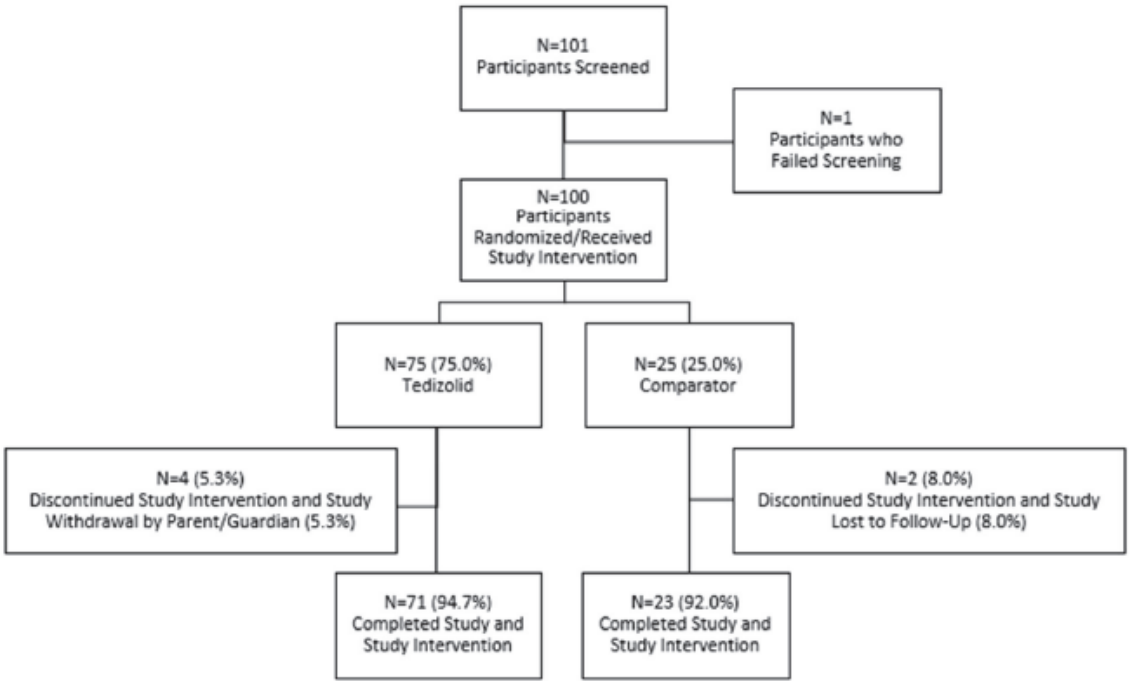
Financial Disclosure

There were no issues identified by the Review Team related to financial disclosure.

Patient Disposition

The disposition of study subjects in Study 018 is shown in Figure 3. Of the 100 subjects randomized to study intervention, 75 (75%) received Tedizolid and 25 (25%) received Comparator therapy. There were 4 (5.3%) subjects who discontinued study intervention in the Tedizolid arm versus 2 (8.0%) in the Comparator arm. These 6 subjects also discontinued from the study. This resulted in 71 subjects (94.7%) who completed the study in the Tedizolid arm versus 23 (92.0%) in the Comparator arm.

Figure 3. Patient Disposition, Study 018



Source: Study 018 CSR - Figure 10-1

Protocol Violations/Deviations

There were at total of 34 protocol violations, two of which were considered to be clinically important. In these two cases, one subject (tedizolid) received study drug that was expired or damaged and the other subject (tedizolid) missed the baseline hematology values from Visit 1.

Demographic Characteristics

As shown in Table 18 below, demographic characteristics in Study 018 were generally similar between treatment arms with a few exceptions as would be expected given the small sample sizes of the study. Approximately 53.0% of subjects in Study 018 were male (53.3% in the Tedizolid arm versus 52.0% in the Comparator arm). The mean age of subjects was 6.0 years (5.9 years in the Tedizolid arm versus 6.4 in the Comparator arm) and the median age was 7.0 years (7.0 years versus 8.0 years). Subjects were stratified and enrolled into 3 cohorts based on age (28 days to < 2 years, 2 to < 6 years, 6 to 12 years) with similar distributions in the two arms due to the stratified randomization by age group. There were some imbalances with respect to race. The majority of subjects were White (80.0%), (77.3% in the Tedizolid arm versus 88.0% in the Comparator arm) with a greater proportion of Black or African American subjects observed in the Tedizolid arm (13.3% versus 4.0%, respectively). The trial was conducted in Europe, the Middle East, Africa, and Latin America, and no subjects were enrolled in the United States.

Table 18. Demographic Characteristics (ITT Population), Study 018

	Tedizolid (N=75) n (%)	Comparator (N= 25) n (%)	Total (N=100) n (%)
Sex			
Male	40 (53.3)	13 (52.0)	53 (53.0)
Female	35 (46.7)	12 (48.0)	47 (47.0)
Age			
Mean years (SD)	5.9 (3.6)	6.4 (3.8)	6.0 (3.6)
Median (years)	7.0	8.0	7.0
Min, max (years)	0.3, 11.0	0.8, 11.0	0.3, 11.0
Age Group			
28 days to < 2 years	15 (20.0)	5 (20.0)	20 (20.0)
2 to 6 years	16 (21.3)	5 (20.0)	21 (21.0)
6 to 12 years	44 (58.7)	15 (60.0)	59 (59.0)
Race			
White	58 (77.3)	22 (88.0)	80 (80.0)
Black or African American	10 (13.3)	1 (4.0)	11 (11.0)
American Indian or Alaska Native	1 (1.3)	0 (0.0)	1 (1.0)
Multiple	6 (8.0)	2 (8.0)	8 (8.0)
Ethnicity			
Hispanic or Latino	13 (17.3)	4 (16.0)	17 (17.0)
Not Hispanic or Latino	62 (82.7)	21 (84.0)	83 (83.0)
Geographic Region			
Europe, Middle East, Africa	63 (84.0)	22 (88.0)	85 (85.0)
Latin America	12 (16.0)	3 (12.0)	15 (15.0)

Source: Partially Adapted from Table 10-3 of the Study 018 CSR
Abbreviations: SD, standard deviation; ITT, intent-to-treat

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

As shown in Table 19, there were no notable differences between treatment arms with respect to other baseline characteristics, taking into account the expected high degree of variability in Study 018 due to small sample sizes. Subjects enrolled in Study 018 had either subcutaneous abscesses (54%), cellulitis (25.0%), wound infections (20.0%) or erysipelas (1%) with similar distributions between study arms. Overall, 84.0% of subjects were inpatients (16% outpatients) with a lower percentage in the Tedizolid arm (80.0% versus 96.0%). The lesion surface area at baseline also tended to be smaller in the Tedizolid arm, (median of 27.0 cm^2 versus 51.0 cm^2 and mean of 60.9 cm^2 versus 65.4 cm^2, respectively).

Table 19. Other Baseline Characteristics (ITT Population), Study 018

	Tedizolid (N=75) n (%)	Comparator (N= 25) n (%)	Total (N=100)
Status at Baseline			
Inpatient	60 (80.0)	24 (96.0)	84 (84.0)
Outpatient	15 (20.0)	1 (4.0)	16 (16.0)
Type of Infection			
Cellulitis	19 (25.3)	6 (24.0)	25 (25.0)
Erysipelas	0 (0.0)	1 (4.0)	1 (1.0)
Subcutaneous Abscess	40 (53.3)	14 (56.0)	54 (54.0)
Wound Infection	16 (21.3)	4 (16.0)	20 (20.0)
Lesion Surface Area (cm^2)			
Mean (SD)	60.9 (144.0)	65.4 (96.0)	62.0 (133.2)
Median	27.0	51.0	28.4
Min, max	2.0, 1068.0	9.0, 480.0	2.0, 1068.0
Prior Antibacterial Drugs			
Yes	17 (22.7)	5 (20.0)	22 (22.0)
No	58 (77.3)	20 (80.0)	78 (22.0)
Baseline Culture			
Positive	52 (69.3)	14 (56.0)	66 (66.0)
Negative	5 (6.7)	6 (24.0)	11 (11.0)

Source: Partially Adapted from Table 10-3 of the Study 018 CSR
Abbreviations: SD, standard deviation, ITT, intent-to-treat

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance in Study 018 was high and similar between treatment arms, with 96.8% mean compliance in the Tedizolid arm versus 98.2% in the Comparator arm.

There were similar proportions of subjects receiving antibacterial therapy for the primary ABSSSI before randomization (17/75 (22.7%) in the Tedizolid arm and 5/25 (20.0%) in the Comparator arm). The most frequently reported concomitant medications were paracetamol (41.0%) and glucose (15%).

Concomitant therapy rules are provided in Table 20 below.

Table 20. Concomitant Therapy Rules, Study 018

Category	Medications and Procedures	Comments on Use
Allowed	Adjunctive aztreonam and/or metronidazole in subjects with wound infection	When gram-negative pathogens are suspected or confirmed
	Supportive measures for optimal medical care (such as debridement, wound packing, wound lavage, aspiration puncture, excision with or without grafting, etc.)	As needed throughout study; detailed information is required to ensure appropriate clinical response categorization
Prohibited	For subject receiving oral study medication, oral topotecan, irinotecan, rosuvastatin, or methotrexate	Prohibited through EOT Visit
	Concomitant systemic antibiotics (except adjunctive aztreonam and/or metronidazole in subjects with wound infections). If therapy is required to treat an infection other than that associated with the primary ABSSSI, such antibiotic therapy should not have overlapping antibacterial activity with the study drug for the pathogen isolated from the ABSSSI lesion at baseline, if possible.	Prohibited through the LFU Visit; prior therapy must be short acting (administration frequency is 1 or more doses per 24 hours), with exception of ≤24 hours prophylactic therapy prior to surgery during the study. Antibiotics without activity against ABSSSI pathogens or those with local activity are allowed.
	Monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin 5-hydroxytryptamine receptor agonists (triptans) and buspirone	Prohibited from 14 days prior to study through the EOT Visit.
	Topical heavy metal extracts such as lead subacetate and mercurial chrome.	Prohibited from Screening through the EOT Visit.

Source: Partially adapted from Table 3 of the Study 018 protocol
Abbreviations: EOT, end of treatment; LFU, late follow-up; ABSSSI, Acute Bacterial Skin and Skin Structure Infections

Efficacy Results – Key Secondary Efficacy Endpoint

The key secondary endpoint was defined as 'Clinical success at the Test of Cure (TOC) visit, 22-29 days after the first infusion, in the ITT and CE-TOC populations'.

As shown in Table 21 below, clinical success rates in the ITT population at the EOT visit (secondary efficacy endpoint) were less favorable in the Tedizolid arm versus the Comparator arm at 94.7% (71/75) versus 100.0% (25/25) (difference: -5.3%, 95% CI: -0.02, -13.4). Clinical

success rates in the ITT population at the TOC visit were 93.3% (70/75) in the Tedizolid arm versus 92.0% (23/25) in the Comparator arm (difference: 1.3%, 95% CI: -10.7, 13.4).

All of the patients in Study 018 who were not assessed as a 'Clinical Success' at EOT or TOC were assessed as 'Indeterminate'. This included 6.7% (5/75) in the Tedizolid arm versus 8.0% (2/25) in the Comparator arm assessed as 'Indeterminate' at the TOC visit. In most of these cases, the reason for the 'Indeterminate' assessment was discontinuation from the study and study intervention (subject either 'Lost to follow-up' or 'Withdrawn by Parent/Guardian'). There were no patients in either arm assessed as a 'Clinical Failure' at either the EOT or TOC visit. Results in age cohort subgroups are discussed below.

Reviewer Comments:

The difference in clinical success rates at the EOT visit favoring the Comparator was not a major concern because success rates at later visits (TOC and LFU) were generally similar and high in both study arms. In addition, the difference in rates at the EOT visit appeared to be due to an imbalance in indeterminate responses unrelated to the therapy received (as opposed to differences in clinical failures) as well as an exceptionally high clinical success rate of 100% in the Comparator arm. Note also that this study was not intended for formal hypothesis testing and that statistical adjustments for multiple comparisons were not considered in estimating the 95% CIs for the treatment differences.

Table 21. Efficacy Analysis- Clinical Response at EOT, TOC, and LFU Visits (ITT and CE-TOC Populations), Study 018

			Tedizolid (N=75) n (%)	Comparator (N= 25) n (%)	Difference in Clinical Success (95% CI)
EOT Assessment (Secondary Efficacy)					
ITT Population					
Clinical Success	71 (94.7)	25 (100.0)	-5.3% (-10.4. -0.2)		
Not a clinical success	4 (5.3)	0 (0.0)			
Clinical Failure	0	0			
Indeterminate	4 (5.3)	0 (0.0)			
CE-TOC Population					
Clinical Success	68 (100)	23 (100)	0.0% (0.0, 0.0)		
Clinical Failure	0	0			
TOC Assessment (Key Secondary Efficacy)					
ITT Population					
Clinical Success	70 (93.3)	23 (92.0)	1.3% (-10.7. 13.4)		
Not a clinical success	5 (6.7)	2 (8.0)			
Clinical Failure	0	0			
Indeterminate	5 (6.7)	2 (8.0)			
CE-TOC Population					
Clinical Success	68 (100)	23 (100)	0.0% (0.0, 0.0)		
Clinical Failure	0	0			
LFU Assessment (Secondary Efficacy)					
CE-TOC Population					
Sustained Clinical Success	68 (100)	23 (100)	0.0% (0.0, 0.0)		
Clinical Relapse	0	0			

Source: Adapted from Study 018 CSR Table 14.2-1, 14.2-2 and 14.2-6.
Note: At the LFU visit, the assessment of clinical relapse was reported as 'sustained clinical success', 'relapse', or 'indeterminate', only in participants who had clinical success at EOT and TOC.
Abbreviations: EOT, end of treatment; LFU, late follow-up; TOC, test of cure; ITT, intent-to-treat; CE-TOC, clinically evaluable at test of cure

Data Quality and Integrity

There were no issues identified regarding data quality and integrity for Study 018. Note that the Office of Scientific Investigations did not inspect any study sites for Study MK-1986-018. Sites were inspected for Study MK-1986-013 and Study MK-1986-014 only. Refer to Section 4.1 of this review for further details.

Efficacy Results – Secondary and other relevant endpoints

As shown in Table 22, 'Early Clinical Response' was slightly lower in the Tedizolid arm versus the Comparator, 80.0% (60/75) versus 84.0% (21/25). However, this difference appeared to be

influenced by a larger percentage of 'Indeterminate' responses in the Tedizolid arm, 14.7% (11/75) versus 0% in the Comparator arm. The 'Failure/Nonresponder' rate was lower in the Tedizolid arm, 5.3% (4/75) versus 16.0% (4/25).

Table 22. Early Clinical Response at the 48-72-Hour Visit (ITT Population), Study 018

	Tedizolid (N=75) n (%)	Comparator (N= 25) n (%)	Difference (95% CI)
Early Clinical Response			
Responder	60 (80.0)	21 (84.0)	
Failure/Nonresponder	4 (5.3)	4 (16.0)	-4.0 (-21.0, 13.0)
Indeterminate	11 (14.7)	0 (0.0)	

Source: Study 018 CSR - Table 14.2-4
Abbreviations: ITT, intent-to-treat; CI, confidence interval

Reviewer Comments:

There were a large number of Indeterminate responses in the Tedizolid arm at the 48-72 hours assessment (visit 3). The reason for several missing lesion measurements appears to be due to Visit 3 being conducted via telephone for outpatients. In Amendment 6, the protocol was modified to reduce the number of required in-person visits during the COVID-19 pandemic.

For the efficacy endpoints of clinical relapses and superinfections, there were no patients with reported clinical relapses or superinfections after the TOC visit.

Microbiological Outcomes
The per-subject microbiological response rate (eradication or presumed eradication) at the TOC visit in the MITT population was 97.8% (45/46) versus 100% (14/14) in the Tedizolid and Comparator arms, respectively, and in the ME population was 100% (45/45) versus 100% (14/14) in the Tedizolid and Comparator arms, respectively. There was one patient in the MITT receiving Tedizolid who had a microbiological response of 'Indeterminate'.

Dose/Dose Response

The dose of tedizolid was determined based on body weight, regardless of age.
- Once-daily 200-mg dose (body weight ≥50 kg), or
- q12h 2 mg/kg doses (body weight ≥30 kg and <50 kg), or
- q12h 2.5 mg/kg doses (body weight 3.2 kg to <30 kg)

Dose response was not evaluated.

Durability of Response

Durability of response was not evaluated in this study because tedizolid was administered to provide treatment during an acute bacterial infection and longer term benefits are unknown.

We note that rates of relapse were monitored at the LFU visit, which occurred 32 to 39 days after the first infusion, and no relapses were observed in the study. We also note that there were no patients assessed as clinical failures at the TOC visit in either treatment arm.

Persistence of Effect

Persistence of effect (or how long the effects of treatment last beyond the period of active treatment) was not evaluated in this study. As previously noted, there were no clinical failures identified at TOC in either treatment group and no relapses at the LFU visit.

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (Patient-Reported Outcome) Endpoints

As an exploratory endpoint, this trial used the Wong-Baker FACES pain rating scale for verbal subjects. For the Wong-Baker endpoint, there were no notable differences across study visits, as shown in Table 23 below. The protocol also mentioned use of a Face, Legs, Activity, Cry, Consolability (FLACC) behavioral pain rating scale for nonverbal subjects, however, analyses of the FLACC data were not reported in the submission.

Table 23. Wong-Baker (ITT Population), Study 018

Visit	Tedizolid (N=75) n (%)	Comparator (N= 25) n (%)	Total (N=100) n (%)
Baseline	N=56	N=19	N=75
Mean (SD)	8.1 (1.70)	7.4 (2.01)	7.9 (1.80)
Median (Range)	8.0 (2 to 10)	8.0 (2 to 10)	8.0 (2 to 10)
48-72 hours	N=56	N=18	N=74
Mean (SD)	4.4 (2.34)	4.2 (2.46)	4.4 (2.36)
Median (Range)	4.0 (0 to 8)	4.0 (0 to 8)	4.0 (0 to 8)
Day 6	N=55	N=19	N=74
Mean (SD)	1.5 (1.86)	2.3 (2.03)	1.7 (1.93)
Median (Range)	0.0 (0 to 6)	2.0 (0 to 6)	2.0 (0 to 6)
Day 10	N=53	N=19	N=72
Mean (SD)	0.3 (0.72)	0.4 (0.84)	0.3 (0.75)
Median (Range)	0.0 (0 to 2)	0.0 (0 to 2)	0.0 (0 to 2)
EOT	N=54	N=19	N=73
Mean (SD)	0.1 (0.38)	0.1 (0.46)	0.1 (0.40)
Median (Range)	0.0 (0 to 2)	0.0 (0 to 2)	0.0 (0 to 2)

Source: Adapted from Table 14.2-23 of the Study 018 CSR
Note: 0= No Hurt, 2= Hurts Little Bit, 4= Hurts Little More, 6=Hurts Even More, 8= Hurts Whole Lot, 10=Hurts Worst
Abbreviations: ITT, intent-to-treat; SD, standard deviation; EOT, end of treatment

Additional Analyses Conducted on the Individual Trial

As shown in Table 24, there were additional analyses of interest conducted for Study 018 for clinical response at the TOC visit for some specific subgroups of patients such as age cohort: (28 days to < 2 years, 2 to < 6 years, 6 to < 12 years) and type of infection (cellulitis, wound infection, abscess), however, these analyses had very few patients per subgroup and were not adequate for detecting possible trends related to these variables. As previously discussed, all nonresponders for this endpoint were due to indeterminate outcomes rather than clinical failures.

Table 24. Subgroup Analyses- Clinical Response at TOC by Age Group and Infection Type (ITT Population), Study 018

Clinical Success Rate at TOC by variable	Tedizolid (N=75)	Comparator (N=25)	Difference in Clinical Success (95% CI)
Age group	**n/N (%)**	**n/N (%)**	
28 mo. to < 2 years	15/15 (100)	5/5 (100)	0.0 (0.0, 0.0)
2 years to < 6 years	14/16 (87.5)	5/5 (100)	-12.5 (-28.7, 3.7)
6 years to 12 years	41/44 (93.2)	13/15 (86.7)	6.5 (-12.2, 25.3)
Infection Type			
Cellulitis	15/19 (78.9)	4/6 (66.7)	12.3 (-29.7, 54.2)
Wound Infection	16/16 (100)	4/4 (100)	0.0 (0.0, 0.0)
Abscess	39/40 (97.5)	14/14 (100)	-2.5 (-7.3, 2.3)

Source: Adapted from Study 018 CSR Table 14.2-24 - 14.2-29
Note: One patient receiving Comparator therapy with erysipelas at baseline is not included in the subgroup analysis by infection type.
Abbreviations: ITT, intent-to-treat; TOC, test of cure

8.2. Integrated Review of Effectiveness

Integrated review of effectiveness across studies was not applicable because the current sNDA presents efficacy results from a single study, Study MK-1986-018.

8.3. Statistical Issues

There were no major statistical issues with Study 018 regarding efficacy noting that the study was primarily a safety and tolerability study and was not designed for hypothesis testing. However, there were some statistical issues as noted below.

One issue was that the efficacy outcomes were generally dominated by 'Indeterminate' assessments (rather than 'Clinical Failure/Nonresponder' assessments). For example, for 'Early Clinical Response', the Tedizolid arm had a greater percentage of subjects with 'Indeterminate' assessments (14.7% (11/75) versus 0% (0/25)) but a smaller percentage of subjects with 'Nonresponder' assessments (5.3% (4/75) versus 16.0% (4/25)). Additionally, for the 'Clinical Success at EOT' and 'Clinical Success at TOC' endpoints, all the subjects who were not assessed

as having 'Clinical Success' had 'Indeterminate' assessments and there were no 'Clinical Failure' assessments.

Another issue which contributed to the above issue was that the study allowed the 48-to72-hour visit (Visit 3) to be conducted via telephone (rather than in-person) for some of the outpatients in the study due to the COVID-19 pandemic. This led to a higher-than-expected percentage of subjects with missing lesion measurements. This made 'Early Clinical Response' less interpretable and worked against the Tedizolid arm which had a greater proportion of outpatients. This is because all subjects with missing lesion measurements (11 subjects) were from the Tedizolid arm and assessed as 'Indeterminate' and counted the same as a 'Nonresponder' in the evaluation of the 'Early Clinical Response' endpoint.

There were also some issues regarding the target population which may limit the generalizability of findings. For example, Study 018 did not include any subjects from U.S. sites and did not include any subjects in Cohort 4 (< 28 days of age).

8.4. Conclusions and Recommendations

Statistical inferences regarding efficacy had limited interpretability in this study due to the relatively small sample size and planned descriptive analysis. However, the descriptive analyses of efficacy endpoints were generally comparable in both study arms and did not raise any major efficacy concerns. In the ITT population, comparisons of clinical success/responder rates for tedizolid versus comparator therapy were 93.3% versus 92.0% for the key secondary efficacy endpoint of clinical success at TOC (with all nonresponses in each arm due to indeterminate outcomes rather than clinical failure) and 80.0% versus 84.0% for the secondary efficacy endpoint of early clinical response, respectively. Note that evidence of efficacy to support the expansion of the ABSSSI indication to include pediatric patients from (b) (4) to less than 12 years of age is based on the extrapolation of evidence from adequate and well-controlled studies in adults, as well as additional pharmacokinetic and safety data in pediatric subjects less than 12 years of age.

9. Clinical Microbiology Review

Tedizolid belongs to the oxazolidinone class of antimicrobial drugs and acts by inhibiting protein synthesis by interacting with the 50S subunit of the bacterial ribosome and inhibiting the initiation phase of translation. A comprehensive assessment of the clinical microbiology information was provided for tedizolid ABSSSI trials in adults (≥18 years of age) and adolescents (12 to <18 years).

Microbiology outcomes in Study 018 were exploratory and included subjects who had an organism isolated at baseline. Of the 100 subjects enrolled in the study, 60 subjects (46 subjects in Tedizolid arm, 14 subjects in the Comparator arm) had a pathogen isolated.

- The most prevalent pathogen in both treatment arms was *Staphylococcus aureus* (82.6% [38/46 subjects] in the Tedizolid arm and 85.7% [12/14] in the Comparator arm). Most of the *S. aureus* pathogens were methicillin susceptible (71.7%). Other baseline pathogens included *Enterococcus faecalis* (4), *Enterococcus faecium* (3), *Staphylococcus haemolyticus* (2), *Streptococcus pyogenes* (2), *Streptococcus constellatus* (2) and *Streptococcus anginosus* group (1) and Group C β-hemolytic streptococcus (1).
- For subjects who had *S. aureus* isolated, clinical success and microbiological eradication were 97.4% in the Tedizolid arm and 100% in the Comparator arm in the MITT Analysis Set. For all pathogens other than *S. aureus,* clinical success and microbiological eradication were 100% in the Tedizolid arm in both the MITT and ME analysis datasets.
- The tedizolid MIC values ranged from 0.12 to > 4 mg/L. Against *S. aureus* isolates, the tedizolid $MIC_{50/90}$ values were 0.5 mg/L and 1 mg/L, respectively, with MIC values ranging from 0.5 to > 4 mg/L. Of the *S. aureus* isolates, 5 isolates had MICs of 1 mg/L and 1 isolate had MIC > 4 mg/L. All isolates other than *S. aureus* had tedizolid MICs ≤ 0.5 mg/L. The tedizolid MICs in Study P018 were similar to tedizolid MICs observed in global surveillance isolates and isolates from the adult and adolescent phase 3 clinical studies.
- There were no isolates that showed decreased susceptibility to tedizolid or emergence of resistance (defined as a >3-fold increase in MIC value from baseline to the MIC value of the pathogen at TOC or LFU).
- There were no instances of superinfection (defined as isolation of a non-baseline pathogen from the primary infection site while the subject was receiving study drug) or emergent new infections (defined as a non-baseline isolate from a post-treatment culture from the primary infection site) in either treatment groups.

There are no revisions to the current approved labeling with respect to clinical microbiology.

10. Review of Safety

10.1. Safety Review Approach

The safety review is primarily based on a phase 3, single-blind, 3:1 randomized, multicenter, active-controlled study (MK-1986-018) of 100 pediatric subjects from birth to less than 12 years of age. However, despite the inclusion criteria of pediatric subjects from birth to 12 years of age in this phase 3 study, the youngest subject enrolled was 4 months old. To supplement the safety database, two phase 1, open-label, pharmacokinetic and safety studies were included. One study enrolled 47 pediatric subjects less than 2 years of age, and the other study enrolled subjects from 2 to <12 years of age. For the safety analysis, Analysis Studio and JMP 17 were

utilized. The Applicant used Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 26.0. Safety evaluations included recording of adverse events, vital signs, and collection of laboratory parameters. AEs included any untoward medical occurrence associated with the use of the drug in humans and whether or not it was considered drug related. Prior safety assessments during the NDA review included an evaluation of oxazolidinone class effects including myelosuppression, lactic acidosis, hypoglycemia, peripheral and ophthalmic neuropathy, drug-drug interactions, and serotonergic effects.

10.2. Review of the Safety Database

Overall Exposure

The Safety Analysis Set (the safety population) in MK-1986-018 included all 100 subjects enrolled in the study, with 75 subjects in the Tedizolid arm and 25 subjects in the Comparator arm. This population is also the same as the ITT population for this study. In the safety population, 94% of the subjects completed study treatment and completed the study per protocol. The majority of subjects were male (53%) and white (80%) with a median age of 7 years and age range of 0.3 to 11 years. The median duration of therapy was 9 days in the Tedizolid arm compared to 10 days in the Comparator arm. The oral formulation of tedizolid used in this study was an oral suspension and is currently not approved by the Agency. The most common initially used comparator drugs were cefazolin (11 subjects, of which 5 transitioned to oral therapy), vancomycin (8 subjects, of which 6 transitioned to oral therapy), and cephalexin (8 subjects, of which 7 transitioned from IV therapy). A greater proportion of subjects in the Comparator arm received treatment for ≥10 days (60%) compared to the Tedizolid arm (20%). Table 25 and Table 26 show the number of subjects in each age cohort and the treatment duration in each arm of the study.

Table 25. Treatment Duration by Age Groups in Tedizolid Arm, Study 018

Tedizolid	<6 days	6 days	>6 days to <10 days	≥ 10 days	Total (N=75)
Birth - <2 years	1	1	9	4	15
2 - <6 years	4	3	5	4	16
6 to <12 years	7	12	18	7	44
Total	12	16	32	15	75

Source: Created by clinical reviewer

Table 26. Treatment Duration by Age Groups in Comparator Arm, Study 018

Comparator	<10 days	10 days to <14 days	>14 days	Total (N=25)
Birth - <2 years	1	4	0	5
2 - <6 years	3	2	0	5
6 to <12 years	6	9	0	15
Total	10	15	0	25

Source: Created by clinical reviewer

Table 27 shows the number of subjects in each study arm that received IV, oral, or IV to oral switch treatment in the tedizolid arm and comparator arm, respectively. The number of IV doses the subjects received in each study group prior to the oral switch is also show in this table. A greater percentage of subjects in the tedizolid arm received oral treatment only (20%) compared to the comparator arm (8%). A higher percentage of subjects in the comparator arm received IV treatment only (28%) compared to the tedizolid arm (7%). The majority of subjects in each arm received a regimen consisting of IV to oral switch – 74% in tedizolid arm compared to 64% in the comparator arm. The comparator arm also had a greater number of subjects receiving IV doses of the antibacterial prior to oral transition with 75% of subjects requiring more than 10 doses of IV antibacterial therapy prior to switch compared with 18% of subjects requiring IV tedizolid prior to an oral switch.

Table 27. IV and Oral Treatment, Study 018

	Tedizolid Arm (N = 75) n (%)	Comparator Arm (N = 25) n (%)	Total N
IV Treatment Only	5 (7)	7 (28)	12
Oral Treatment Only	15 (20)	2 (8)	17
IV to Oral Switch	55 (73)	16 (64)	71
Number of IV doses prior to Oral Switch			
	Tedizolid IV to Oral Switch (N = 55)	**Comparator IV to Oral Switch (N = 16)**	**Total N**
1 – 2 doses	2 (4)	0	2
3 – 6 doses	25 (45)	0	25
7 – 10 doses	18 (33)	4 (25)	22
> 10 doses	10 (18)	12 (75)	22

Source: Created by clinical reviewer
Abbreviations: IV, intravenous

To supplement the tedizolid exposure in the pediatric population, particularly for the younger age cohort, the submission also included two phase 1 PK studies (MK-1986-013 and MK-1986-014) evaluating the PK data of single dose PO and single and multiple doses of IV tedizolid in pediatric subjects. MK-1986-014 included subjects aged birth to < 2 years of age and MK-1986-013 included subjects aged 2 to <12 years of age. Since the phase 3 study (MK-1986-018) did not enroll subjects younger than 4 months, MK-19860-014 provided additional exposure and safety data on subjects who were younger than 4 months of age. Based on the cohort subjects were randomized into, they received either a single dose or multiple doses of IV tedizolid or a single dose of PO tedizolid. There were a total of 38 out of the 47 subjects who were less than 4 months of age who received tedizolid. Of these 38 subjects, 21 received a single IV dose, 8 received multiple IV doses, and 9 received a single oral dose. Table 28 presents the number and ages of subjects exposed to tedizolid in the two phase 1 studies. Preterm neonates were defined as an infant born between 26 weeks and 37 weeks gestation. Full term neonates were born after 37 weeks gestation. In both studies, 24 subjects received the oral formulation of

tedizolid and a total of 45 subjects received the IV formulation. The oral formulation of tedizolid used in this study was an oral suspension and is currently not approved by the Agency.

Table 28. Number of Subjects Receiving IV or PO Tedizolid, Study 013 and 014

Study	Drug Route	Dosing	Age Range/Group	N
MK-1986-014	IV	Single dose	28 days to <6 months	4
			6 months to <24 months	6
			Birth to <28 days (full term)	8
			Birth to <28 days (preterm neonates)	9
		Multiple dosing	Birth to <28 days (full term)	4
			Birth to <28 days (preterm neonates)	4
	PO	Single dose	Birth to <28 days (full term neonates)	4
			Birth to <28 days (preterm neonates)	4
			28 days to <24 months	4
MK-1986-013	IV	Single dose	2 to <6 years	5
			6 to <12 years	5
	PO		2 to <6 years	6
			6 to <12 years	6

Source: Created by clinical reviewer.
Abbreviations: IV, intravenous; PO, oral

Adequacy of the safety database:

The safety population for this submission includes all patients who have received the proposed weight-based dosages of IV and oral tedizolid. Overall, the safety database is adequate for review.

10.3. Adequacy of Applicant's Clinical Safety Assessments

The safety population for this study consists of all subjects who received at least one dose of the study treatment. In the pediatric study, the safety was evaluated based on AEs, physical examination, laboratory data, vital signs, and basic neurologic examination with cranial nerve assessments. Subjects were followed for 35 days after receiving the study drug for development of any AEs, unless monitored for an AE. All AEs that occurred during the trial were recorded in the case report forms. All treatment-emergent adverse events (TEAEs) that, in the opinion of the investigator, may have been infusion related were identified as such on the AE case report form. Overall, the Applicant's clinical safety assessment is adequate for review.

Issues Regarding Data Integrity and Submission Quality

There were no issues identified with the integrity or submission quality of the data. Data were submitted in standardized formats for review.

Categorization of Adverse Events

The Applicant used MedDRA (v26.0), coding to map investigator terms to preferred terms. A TEAE was defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of the study (tedizolid or comparator) drug. All AEs reported in this study met the definition of TEAE.

Routine Clinical Tests

The laboratory tests performed were done in accordance with the PK profile, known AEs of the drug, and visit schedule. Changes from baseline were reported.

10.4. Safety Results

Deaths

There were no deaths in Studies MK-1986-018, MK-1986-013, and MK-1986-014.

Serious Adverse Events

There were no SAEs in Study MK-1986-018. There were also no SAEs in Studies MK-1986-013 and MK-1986-014 related to the study drug.

Dropouts and/or Discontinuations Due to Adverse Events

There were no dropouts or discontinuations from Study MK-1986-018 due to adverse effects. There were four subjects in the tedizolid arm who were withdrawn by a parent/guardian, but no additional details were provided. In the comparator arm, there were two patients who were lost to follow up. There were also no dropouts or discontinuations from Studies MK-1986-013 and MK-1986-014.

Significant Adverse Events

In Study MK-1986-018, there was one subject in the tedizolid arm who experienced level 3 thrombocytopenia (<100,000 cells/L) during the course of the study. There were no changes made to the study drug regimen, and the subject's platelets recovered to within normal range by TOC.

Treatment Emergent Adverse Events

In Study MK-1986-013, the most common TEAEs overall were vomiting in 3 subjects with one receiving IV tedizolid and 2 receiving oral tedizolid. Pyrexia was also seen in 3 subjects, also with one receiving IV tedizolid and 2 receiving PO tedizolid. In Study MK-1986-014, eight subjects (17%) reported AEs with one subject with a drug related AE (immature granulocyte increase) after a single oral dose. The other AEs reported that were unrelated to the study drug were anemia, swelling of eyelid, incomplete response to therapeutic product, conjunctivitis, pneumonia, and *Serratia* sepsis.

In Study MK-1986-018, a slightly increased total rate of TEAEs was seen in the tedizolid phosphate arm versus the comparator arm (28% versus 24%, respectively), as shown in Table 29. TEAEs in both arms were primarily made up of those with mild severity. There were no severe AEs, SAEs, or deaths in either treatment arm.

Table 29. Overview of Treatment Emergent Adverse Events, Safety Population, Study 018

	Tedizolid Phosphate (N=75)	Comparator (N=25)
Any AE	21 (28)	6 (24)
Mild	19 (25)	6 (24)
Moderate	9 (12)	1 (4)
Severe	0	0
SAEs	0	0
SAEs with fatal outcome	0	0
Life threatening SAEs	0	0
AE leading to permanent discontinuation	0	0
AE leading to dose modification		
Dose not changed	12 (16)	5 (20)
Drug interrupted	1 (1)	0

Source: Created by clinical reviewer. Source: OCS Analysis Studio, Custom Table Tool.
Treatment-emergent adverse events defined as any adverse event that occurred after treatment began.
Abbreviations: SAEs, serious adverse event; AE, adverse event

Table 30 below presents the TEAEs by system organ class (SOC) and preferred terms for Study MK-1986-018. The rates of TEAE between both arms of the study are comparable with 28% of subjects in the Tedizolid arm experiencing any TEAE compared to 24% of subjects in the Comparator arm. The most frequently identified TEAE in the Tedizolid arm was rash (5%), which also occurred frequently in the Comparator arm (8%). The most commonly reported SOC was infections and infestations; TEAEs under this SOC occurred in 17% in the Tedizolid arm compared to 8% in the Comparator arm; folliculitis was the most common TEAE, occurring in 4% of those in the Tedizolid arm and none in the Comparator arm. Gastrointestinal (GI) disorders also had higher rates occurring in both arms, with 9% of subjects in the Tedizolid arm and 16% of subjects in the Comparator arm experiencing any GI related TEAEs. In the Tedizolid arm, nausea and vomiting were the most common gastrointestinal disorders (4% each), while diarrhea (12%), nausea (4%) and constipation (4%) were most common in the Comparator arm.

While the overall rates of TEAEs were slightly higher in the Tedizolid arm compared to the Comparator arm, some of the reported TEAEs were likely unrelated to the study drugs particularly in the infections and infestations SOC category. Common TEAEs that are associated with antibacterial study drugs – predominantly in the gastrointestinal disorders – were higher in

the Comparator arm compared to the Tedizolid arm. In this small population comparing tedizolid and comparator, the overall safety of tedizolid is comparable to other comparator drugs in this study.

Table 30. Summary of TEAEs by System Organ Class and Preferred Terms, Safety Population, Study 018

System Organ Class Preferred Term	Tedizolid N = 75 n (%)	Comparator N = 25 n (%)
Any TEAE	21 (28)	6 (24)
Infections and infestations	13 (17)	2 (8)
Folliculitis	3 (4)	0
Skin Infection	2 (3)	0
Upper respiratory tract infection	2 (3)	1 (4)
Conjunctivitis	1 (1)	0
Diarrhea	1 (1)	0
Gastroenteritis	1 (1)	0
Influenza	1 (1)	0
Nasopharyngitis	1 (1)	0
Oral pustule	1 (1)	0
Viral Infection	1 (1)	0
Gastrointestinal disorders	7 (9)	4 (16)
Nausea	3 (4)	3 (4)
Vomiting	3 (4)	0
Abdominal Pain	1 (1)	0
Diarrhea	1 (1)	3 (12)
Gastric disorder	1 (1)	0
Gingival ulceration	1 (1)	0
Constipation	1 (1)	1 (4)
Skin and subcutaneous tissue disorders	5 (7)	3 (12)
Rash	4 (5)	2 (8)
Erythema	1 (1)	0
Alopecia	0	1 (4)
Miliaria	0	1 (4)
Respiratory, thoracic, and mediastinal disorders	4 (5)	0
Rhinitis allergic	2 (3)	0
Atelectasis	1 (1)	0
Dysphonia	1 (1)	0
Nasal Congestion	1 (1)	0
Vascular disorders	3 (4)	0
Phlebitis	2 (3)	0
Pallor	1 (1)	0

System Organ Class Preferred Term	Tedizolid N = 75 n (%)	Comparator N = 25 n (%)
Blood and lymphatic system disorders	2 (3)	0
Thrombocytosis	2 (3)	0
Neutropenia	1 (1)	0
Thrombocytopenia	1 (1)	0
Eye disorders	2 (3)	0
Astigmatism	1 (1)	0
Conjunctivitis	1 (1)	0
Visual acuity reduced	1 (1)	0
General disorders and administration site conditions	2 (3)	0
Catheter site pain	1 (1)	0
Fatigue	1 (1)	0
Infusion site extravasation	1 (1)	0
Injury, poisoning, and procedural complications	2 (3)	1 (4)
Accidental overdose	1 (1)	0
Scratch	1 (1)	0
Thermal burn	0	1 (4)
Investigations	2 (3)	1 (4)
Aspartate aminotransferase increased	1 (1)	1 (4)
White blood cell count increased	1 (1)	0
Musculoskeletal and connective tissue disorders	2 (3)	0
Arthralgia	1 (1)	0
Myalgia	1 (1)	0
Metabolism and nutrition disorders	2 (3)	2 (8)
Decreased appetite	1 (1)	2 (8)
Dehydration	1 (1)	0
Product issues	1 (1)	0
Device occlusion	1 (1)	0
Psychiatric disorders	1 (1)	0
Nightmare	1 (1)	0

Source: Created by Clinical Reviewer
Rash includes dermatitis allergic, dermatitis contact, Dermatitis diaper, Rash erythematous, Rash maculo-papular.
Conjunctivitis includes Conjunctivitis, Conjunctivitis allergic.
Diarrhea includes Diarrhea, Diarrhea viral.
Skin infection includes Impetigo, Skin infection
Abbreviations: TEAE, treatment-emergent adverse event

Laboratory Findings

In studies MK-1986-013 and MK-1986-014, there were no common laboratory findings associated with tedizolid.

Hematology
In Study MK-1986-018, there was one subject in the Tedizolid arm with level 3 thrombocytopenia (with a platelet count of <100,000 cells/L) that developed during the course of the study versus zero in the comparator arm. No adjustments were made to the drug regimen. On follow up laboratory evaluation, the subject recovered their platelet count to within the normal range by TOC. There were no subjects in the Tedizolid arm who had neutropenia (absolute neutrophil count falling to <50% of the lower limit of normal for age) or anemia (hemoglobin falling to <75% of the lower limit of normal for age).

Liver Tests
There were no cases of elevation of liver enzymes or of bilirubin in either the Tedizolid or Comparator arms in Study MK-1986-018

Electrolytes
In Study MK-1986-018, there was one subject in the tedizolid arm with level 3 hypoglycemia (<40 mg/dL) that developed during the course of the study. No adjustments were made to the drug regimen. On follow up laboratory evaluation, hypoglycemia resolved.

Vital Signs

Vital signs, including temperature, pulse rate, systolic blood pressure, and diastolic blood pressure were monitored during all three studies. There were no potentially clinically significant changes, and the vital signs were comparable between the Tedizolid and Comparator groups over time.

Electrocardiograms

Electrocardiograms were not obtained during the studies.

QT

This is not applicable to the submission.

Immunogenicity

This is not applicable to the submission.

10.5. Analysis of Submission-Specific Safety Issues

Safety concerns associated with the oxazolidinone drug class include myelosuppression, serotonin syndrome, optic neuropathy, lactic acidosis, peripheral neuropathy, drug interactions, and *Cloistridiodes difficile* infection. There were no TEAEs related to these safety concerns identified in Studies MK-1986-018, MK-1986-013, and MK-1986-014.

10.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable.

10.7. Safety Analyses by Demographic Subgroups

The demographic characteristics of Study 018 are shown in Table 31. This study enrolled subjects who were predominantly male (53%), white (80%), and Eastern European (73%) with a median age of 7 years and range of 0.3 to 11 years. While there was a limited sample size, there were no notable differences in safety signals in pediatric subjects aged less than 12 years compared to adolescents and adults and no differences noted in frequency of AEs among the demographic subgroups.

Table 31. Demographic Characteristics of the Safety Population, Study 018

Characteristic	Tedizolid Arm N = 75	Comparator Arm N = 25	Total N = 100
Sex, n (%)			
Female	35 (47)	12 (48)	47 (47)
Male	40 (53)	13 (52)	53 (53)
Age, n (%)			
4 months <2 years	15 (20)	5 (20)	20 (20)
2 years to <6 years	16 (21)	5 (20)	21 (21)
6 years <12 years	44 (59)	15 (60)	59 (59)
Race, n (%)			
American Indian/Alaskan Native	1 (1)	0	1 (1)
Black or African American	10 (13)	1 (4)	11(11)
Multiple	6 (8)	2 (8)	8 (8)
White	58 (77)	22 (88)	80 (80)
Country of Participation, n (%)			
Bulgaria	32 (43)	10 (40)	42 (42)
Georgia	7 (10)	4 (16)	11 (11)
Guatemala	10 (13)	2 (8)	12 (12)
Latvia	1 (1)	0	1 (1)
Lithuania	1 (1)	1 (4)	2 (2)
Mexico	2 (3)	1 (4)	3 (3)
Russian Federation	2 (3)	1 (4)	3 (3)
South Africa	10 (13)	1 (4)	11 (11)
Turkey	1 (1)	0	1 (1)
Ukraine	9 (12)	5 (20)	14 (14)

Source: Created by Clinical Review via OCS Analysis Studio, Custom Table Tool

10.8. Specific Safety Studies/Clinical Trials

There were no specific safety studies for review.

10.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

This is not applicable to this submission.

Human Reproduction and Pregnancy

Not applicable to this submission.

Pediatrics and Assessment of Effects on Growth

Not applicable as this drug is not intended for long-term use.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This is not applicable to the drug product.

10.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Post-approval labeling changes for tedizolid include the addition of a Drug Interactions section describing that orally administered tedizolid inhibits breast cancer resistance protein (BCRP) in the intestine, which can increase the plasma concentrations of orally administered BCRP substrates, with the potential for adverse reactions. The Adverse Reactions section was updated to include thrombocytopenia, and infusion-related adverse reactions.

Expectations on Safety in the Postmarket Setting

Tedizolid has undergone postmarketing surveillance since its approval including monitoring for myelosuppression, serotonin syndrome, peripheral neuropathy, optic neuropathy, lactic acidosis, and emergence of drug resistance.

10.11. Integrated Assessment of Safety

Seventy-five pediatric subjects aged 4 months to less than 12 years of age with ABSSSI were exposed to tedizolid in a randomized, single-blind, multicenter, active-control study. To increase the safety database of pediatric subjects, an additional 69 subjects from two phase 1 studies were included in the safety review. Of note, 38 subjects in Study 014 were less than 4 months old to supplement the lack of pediatric subjects younger than 4 months in Study 018.

In Study 018 the most common adverse reactions were infusion- or injection-related adverse reactions (including catheter site pain, catheter occlusion, infusion site extravasation, phlebitis; 5%), vomiting (4%), and thrombocytosis (2%). The rate of infusion- or injection-related adverse reactions in this study was consistent with the rate of these reactions noted in the adult population at 4%. The safety profile of tedizolid in Study 018 was similar to that seen in the adolescent and adult clinical trials. There were no deaths and no significant safety concerns identified. There was only one case of hypoglycemia but otherwise, no cases of lactic acidosis, optic neuritis, or *C. difficile* infection, as noted with other members of the class of oxazolidinones.

No unexpected safety signals were identified in subjects younger than 4 months in Study 014. Overall, the safety profile for tedizolid in pediatric subjects less than 12 years of age appears comparable to that of adolescents and adults.

10.12. Conclusions and Recommendations

The Applicant has provided adequate evidence to expand the ABSSSI indication to the new population of pediatric patients from (b) (4) to less than 12 years of age. Based on similarities in PK, ABSSSI pathophysiology and microbiology in adult and pediatric patients, the pediatric studies submitted in these sNDAs support the extrapolation of efficacy of tedizolid from adults including the efficacy of IV tedizolid down to birth and the oral tablet to pediatric patients weighing at least 35 kg. No new safety signals were identified in the pediatric population studied and the overall safety profile of tedizolid appears similar in the pediatric and adult populations.

11. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this sNDA as there were no issues that needed input from external experts.

12. Pediatrics

Tedizolid was approved for ABSSSI in adults on June 20, 2014, and for adolescents aged 12 years to less than 18 years on June 16, 2020. This submission fulfils PREA PMRs 2159-7 and 2159-5 and expands approval of IV tedizolid to pediatric patients down to birth and also the oral tablet formulation to include pediatric patients weighing at least 35 kg. Please refer to Section 15 for additional PREA PMR studies issued for this drug.

13. Labeling Recommendations

13.1. Prescription Drug Labeling

Prescribing Information

This prescribing information (PI) review includes a high-level summary of the rationale for major changes incorporated into the finalized PI (the PI that will be approved or is close to being approved) compared to the PI submitted on June 6, 2024. The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidances, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 32. Major Labeling Changes with Associated Rationale

Full Prescribing Information Sections	Applicant-Proposed Labeling	Rationale or Major Changes Incorporated into the Finalized Prescribing Information (PI)
1 Indications and Usage	Applicant deleted 12 years of age and older.	Subsection 1.1 “Acute Bacterial Skin and Skin Structure Infections” of the PI: Agreed with removal. Added “at least 26 weeks gestational age and weighing at least 1 kg” to the indication statement in subsection to align with study data and results. Refer to Sections 6 and 8 of this Multi-disciplinary Review for additional details.
2 Dosage and Administration	Applicant updated dosage and administration information and added weight-based dosing information with referral to Table 2 for details.	Subsection 2.1 “Important Administration Instructions for Pediatric Patients Weighing Less than 35 kg,” of the PI: Added information to exclude administration of oral tablet to pediatric patients weighing less than 35 kg.
	Applicant added table 2 for Intravenous Dosage of SIVEXTRO for Pediatric Patients weighing less than 35 kg	Subsection 2.3 “Recommended Dosage for Pediatric Patients” of the PI: Applicant’s table 2 was edited to provide clarity and revision of

Full Prescribing Information Sections	Applicant-Proposed Labeling	Rationale or Major Changes Incorporated into the Finalized Prescribing Information (PI)
		intravenous dosage of SIVEXTRO for pediatric patients weighing 1 kg to less than 2 kg per clinical information amendment previously submitted. Added the gestational age and lower weight limit (at least 26 weeks gestational age and weighing at least 1 kg) to further specify age and weight for which SIVEXTRO for injection is indicated. Refer to Section 6 of this Multidisciplinary Review for additional information. Created an extra table 3 for oral tablet dosage of SIVEXTRO for pediatric patients with ABSSSI weighing greater than or equal to 35 kg, and also added language to not administer SIVEXTRO tablets to pediatric patients weighing less than 35 kg as this was not studied. Subsection 2.4 Recommendations regarding Missed Dose(s): Added additional recommended instructions regarding missed doses. Refer to Sections 6 and 8 of this Multidisciplinary Review for additional details regarding the changes outlined above for this section of the PI.
6 Adverse Reactions	Applicant added information on clinical trials experience in pediatric patients including serious adverse events, laboratory parameters and updated tables to include the new pediatric study results	Subsection 6.1, subheading Clinical Trials Experience in Pediatric Patients of the PI: Did not agree with (b) (4) [redacted]

Full Prescribing Information Sections	Applicant-Proposed Labeling	Rationale or Major Changes Incorporated into the Finalized Prescribing Information (PI)
		Recommended separating the clinically significant laboratory abnormalities by clinical trial (b) (4) [redacted] With the limited number of laboratory abnormalities, a descriptive paragraph was used instead. Disclaimer was added to avoid implying an unapproved dosage form and/or dosage. Refer to Section 10 of this Multidisciplinary Review for additional details.
8 Use in Specific Populations	Applicant revised subsection 8.4 to expand pediatric population age and remove language regarding the safety and effectiveness not being established in pediatric patients aged below 12 years.	Subsection 8.4 "Pediatric Use" was revised based on the labeling recommendations in the Guidance for Industry: Pediatric Information Incorporated into Human Prescription Drug and Biological Product Labeling (March 2019). Additions were made to include at least 26 weeks gestational age and weight greater than 1 kg in the approved use statement. Added unapproved use statement for pediatric patients less than 26 weeks gestational age and weighing less than 1 kg.
12 Clinical Pharmacology	(b) (4) [redacted]	
14 Clinical Studies	Applicant added information from the pediatric studies	Recommended to add statement to reflect that while the oral suspension

Full Prescribing Information Sections	Applicant-Proposed Labeling	Rationale or Major Changes Incorporated into the Finalized Prescribing Information (PI)
		was used in the clinical trials, the oral formulation is not currently approved.
Sections 3 Dosage forms and Strengths, 11 Description and 16 How Supplied and Storage		Added identifying characteristics to section 16. Refer to Section 4.2 of this review for additional information.

Source: Reviewer
Abbreviations: ABSSSI, Acute Bacterial Skin and Skin Structure Infections, CV, coefficient of variation

Approved Labeling Types

Upon approval of this Application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Information
- Carton and Container Labeling

14. Risk Evaluation and Mitigation Strategies

No new risk evaluation and mitigation strategies are need for this sNDA.

15. Postmarketing Requirements and Commitment

This sNDA fulfills the following postmarketing requirements:

- PMR 2159-7: Conduct a Randomized, Single Blind, Multicenter Safety and Efficacy Study of Intravenous to Oral SIVEXTRO (tedizolid phosphate) and Intravenous to Oral Comparator for the Treatment for Acute Bacterial Skin and Skin Structure Infections in Pediatric Patients Aged Birth to <12 Years
- PMR 2159-5: Conduct a Phase 1 Single-Dose Safety and Pharmacokinetic Study of Oral and Intravenous SIVEXTRO (tedizolid phosphate) in Inpatients Under 2 Years Old.

The following postmarketing study is required:

- PMR 4827-1: Complete development of the [redacted] (b) (4) formulation including product stability studies – long-term and accelerated storage, stress studies, and applicable in-use stability and compatibility.

16. Division Director (Clinical) Comments

I agree with the review team's assessment and recommendations.

17. Appendices

17.1. References

Jenkins, TC, AL Sabel, EE Sarcone, CS Price, PS Mehler, and WJ Burman, 2010, Skin and soft-tissue infections requiring hospitalization at an academic medical center: opportunities for antimicrobial stewardship, Clin Infect Dis, 51(8):895-903.

Li D, Sabato PE, Guiastrennec B, Ouerdani A, Feng HP, Duval V, De Anda CS, Sears PS, Chou MZ, Hardalo C, Broyde N, and R ML., 2021, Population Pharmacokinetics, Exposure-Response, and Probability of Target Attainment Analyses for Tedizolid in Adolescent Patients with Acute Bacterial Skin and Skin Structure Infections., Antimicrobial Agents and Chemotherapy, 65 (12).

FDA Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling (March 2019)

Schwartz, GJ and SL Furth, 2007, Glomerular filtration rate measurement and estimation in chronic kidney disease, Pediatr Nephrol, 22(11):1839-1848.

Schwartz, GJ, A Muñoz, MF Schneider, RH Mak, F Kaskel, BA Warady, and SL Furth, 2009, New equations to estimate GFR in children with CKD, J Am Soc Nephrol, 20(3):629-637.

Spellberg, B, GH Talbot, HW Boucher, JS Bradley, D Gilbert, WM Scheld, J Edwards, Jr., and JG Bartlett, 2009, Antimicrobial agents for complicated skin and skin-structure infections: justification of noninferiority margins in the absence of placebo-controlled trials, Clin Infect Dis, 49(3):383-391.

Talan, DA, A Krishnadasan, RJ Gorwitz, GE Fosheim, B Limbago, V Albrecht, and GJ Moran, 2011, Comparison of Staphylococcus aureus from skin and soft-tissue infections in US emergency department patients, 2004 and 2008, Clin Infect Dis, 53(2):144-149.

17.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): MK-1986-018, MK-1986-014, MK-1986-013

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 177		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

17.3. Nonclinical Pharmacology/Toxicology

Long-term carcinogenicity studies have not been conducted with tedizolid phosphate.

17.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

17.4.1. Clinical Pharmacology Studies

17.4.1.1. Pediatric Phase 1 Clinical Trial With a Single Dose

Study MK-1986-013

Study MK-1986-013 was a phase 1, two-part, open-label, nonrandomized, multicenter study to assess the PK, safety, and tolerability, of a single dose of tedizolid phosphate in pediatric subjects aged 2 to <12 years of age receiving prophylaxis for or with a confirmed or suspected infection with gram-positive bacteria and receiving concurrent antibacterial drug treatment with gram-positive activity. Subjects were divided into 6 age-and-dose-based cohorts and administered tedizolid phosphate according to the weight-based doses summarized in Table 33.

The dosages for this study, shown in Table 33 were selected with the objective of determining PK in pediatric subjects aged 2 to <12 years of age with the goal of determining a dosage which would achieve plasma exposures (as tedizolid area under the curve, AUC) similar to those observed in adults receiving the therapeutic dose.

Table 33. Planned Age Cohorts and Corresponding Tedizolid Phosphate Weight-Based Doses

Part	Group	Cohort	Age (years)	Weight based dose (mg/kg)*	Route (Formulation)	Frequency
A	1	1	6 to <12	5	IV (powder for reconstitution for IV infusion over 1 hour)	Once
		2		4		
	2	1	2 to <6	6		
		2		3		
B	3		6 to <12	4	Oral (PFOS formulation)	
	4		2 to <6	3		

Source: Synopsis Applicant's Report for Study MK-1986-013.
* Dose modifications were performed based on interim PK and modeling/simulation analyses.
Abbreviations: IV, intravenous; PFOS, powder for oral suspension.

Of the 37 subjects screened, 32 were enrolled in the study, and received a single dose of tedizolid phosphate. One participant in Group 2 Cohort 1 discontinued the trial and was lost to follow-up after having received study medication per protocol. All enrolled subjects were included in the intention to treat, safety, and pharmacokinetic (PK) analysis populations. Patient demographic information for Study MK-1986-013 is shown in Table 46. Overall, tedizolid phosphate appeared to be well tolerated across all cohorts. For additional details on the safety and tolerability of tedizolid phosphate in the clinical trial population, please see Section 10.

The PK analysis population was comprised of all 32 enrolled subjects. Eight PK samples were planned for study Day 1 for both Parts of the study. The schedule for PK sample collection (0.5 mL of blood per sample) was as follows: (1) in the IV cohorts, immediately after the end of the 1 hour infusion, and between 1.5 to 24 hours post-infusion; (2) in the oral suspension cohorts, between 1 to 24 hours post-administration. PK samples were analyzed using a previously validated bioanalytical method (see Section 17.4.2 for details on in-study method performance). PK data obtained from this study was used to update the existing popPK models for tedizolid phosphate and tedizolid to predict drug exposures in pediatric subjects (See Section 17.4.3).

The estimated mean steady state PK parameters from noncompartmental analyses are summarized by cohort in Table 34. Note that PK parameters could not be estimated for tedizolid phosphate following oral administration due to the lack of quantifiable concentration observations. When administered by IV, systemic tedizolid phosphate was detected, however it rapidly converted to tedizolid, as shown by the tedizolid T_{max} approaching the end of infusion time. Mean tedizolid systemic exposures increased in approximately a dose-proportional manner with increasing doses within an age-range group, and exposures were similar between groups when normalized for the dose administered. Similar exposures were observed for IV and orally administered tedizolid phosphate (measured as tedizolid AUC), and the absolute bioavailability of the powder for oral suspension formulation was estimated to be 112% (95% CI: 0.93-1.35).

Table 34. Summary of Geometric Mean (95% Confidence Interval) of PK Parameters for Tedizolid Phosphate and Tedizolid Across Cohorts

Tedizolid Phosphate						
Group Cohort	**Age range (years)**	**Dose**	**Number**	**$AUC_{0\text{-last}}$ (h*ng/mL)**	**$AUC_{0\text{-}\infty}$ (h*ng/mL)**	**C_{max} (ng/mL)**
1-1	6 to <12	5 mg/kg (IV)	4	64.8 (6.42, 654)	NR	76.3 (8.38, 695)
1-2	6 to <12	4 mg/kg (IV)	5	63.6 (8.04, 503)	NR	82.4 (11.4, 595)
2-1	2 to <6	6 mg/kg (IV)	5	433 (54.8, 3430)	NR	710 (98.4, 5130)
2-2	2 to <6	3 mg/kg (IV)	4	182 (18.1, 1840)	NR	234 (25.7, 2140)
3	6 to <12	4 mg/kg (oral)	6	*	NR	*
4	2 to <6	3 mg/kg (oral)	6	*	NR	*
Tedizolid						
Group Cohort	**Age range (years)**	**Dose**	**Number**	**$AUC_{0\text{-last}}$ (h*ng/mL)**	**$AUC_{0\text{-}\infty}$ (h*ng/mL)**	**C_{max} (ng/mL)**
1-1	6 to <12	5 mg/kg (IV)	5	28200 (21200, 37600)	29600 (22500, 38900)	4960 (3440, 7140)
1-2	6 to <12	4 mg/kg (IV)	5	19700 (14800, 26200)	21000 (16000, 27600)	4140 (2880, 5970)
2-1	2 to <6	6 mg/kg (IV)	5	26800 (20200, 35800)	27300 (20800, 35900)	7460 (5180, 10800)
2-2	2 to <6	3 mg/kg (IV)	5	17100 (12800, 22700)	17300 (13200, 22700)	4190 (2910, 6030)
3	6 to <12	4 mg/kg (oral)	6	22700 (17500, 29500)	24900 (19400, 32000)	2590 (1860, 3620)
4	2 to <6	3 mg/kg (oral)	6	14600 (11200, 18900)	17200 (13100, 22600)	1820 (1310, 2550)

Source: Reviewer compiled from Table 11-1 and 11-2 from Applicant's Report for Study MK-1986-013.
*Unable to estimate PK parameters for Tedizolid Phosphate, as less than 2 quantifiable concentrations per subject.
Abbreviations: PK, pharmacokinetic; CI, confidence interval; NR, not reported; IV, intravenous

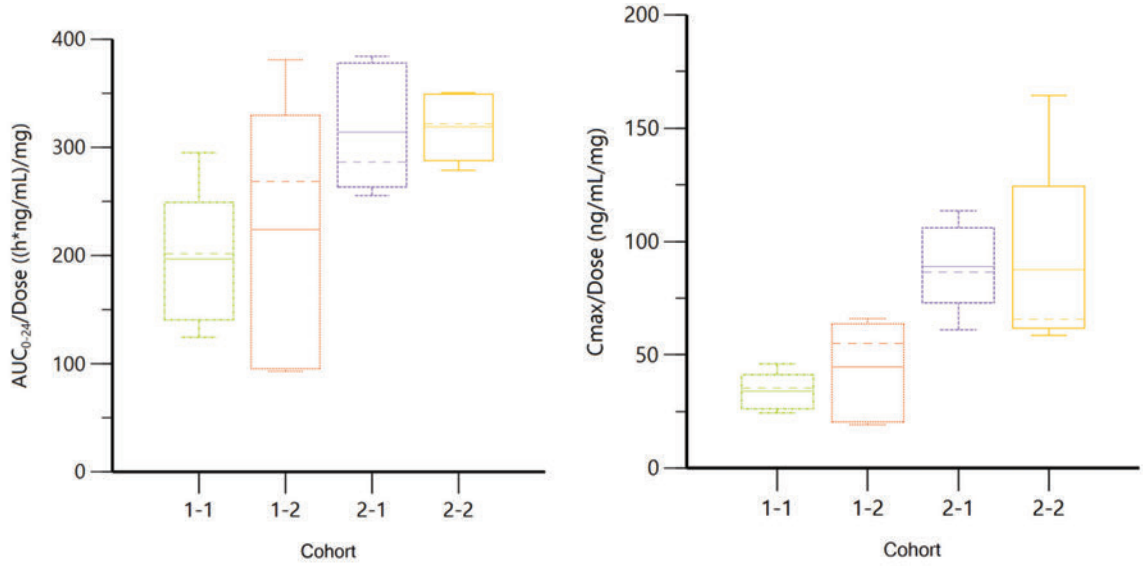
Reviewer comment:

The Applicant's overall PK parameter findings from this study are consistent with the reviewer's analysis. We note that two subjects in Group 3 receiving oral suspension had an observed

adverse event of vomiting recorded, however the study report did not discuss the observation, and the subjects were included in the analysis PK dataset. The vomiting occurred more than 24 hours after study drug administration and therefore does not impact the PK parameters for these subjects.

Subjects aged 6 to <12 years of age received 5 mg/kg in Cohort 1-1, and 4 mg/kg in Cohort 1-2. However subjects aged 2 to <6 years of age received 6 mg/kg in Cohort 2-1, and 3 mg/kg in Cohort 2-2. Due to the differing dosage administered to the two age groups in the study, the Reviewer plotted dose-normalized AUC_{0-24} and C_{max} to compare exposure across age groups (Figure 4) to determine if any differences were attributable to the age-and-dosage Cohorts. When normalized for dose, slightly higher mean C_{max} /Dose was observed for subjects 2 to <6 years of age (Cohort 2), compared to subjects 6 to <12 years of age (Cohort 1), however the interquartile range of normalized exposure for area under the curve over 24 hours, AUC_{0-24}, overlapped for all cohorts. In the original NDA submission for tedizolid for ABSSSI, AUC_{0-24} was the exposure metric associated with efficacy. The Applicant proposed twice daily dosing to reduce the unit dose administered. The C_{max} for the final recommended dosage is less than the 95th percentile observed in adults in the Phase 3 study when administered the dosage associated with efficacy, therefore, the C_{max} trend shown in Figure 4 appears clinically insignificant.

Figure 4. Boxplots of Dose-Normalized Area Under the Curve to Infinity and Dose-Normalized Maximum Concentration Across Single-Dose IV Infusion Cohorts



Source: Reviewer analysis.
1-1: Subjects 6 to <12 years of age administered 5 mg/kg tedizolid phosphate by IV once;
1-2: Subjects 6 to <12 years of age administered 4 mg/kg tedizolid phosphate by IV once;
2-1: Subjects 2 to <6 years of age administered 6 mg/kg tedizolid phosphate by IV once;
2-2: Subjects 2 to <6 years of age administered 3 mg/kg tedizolid phosphate by IV once; AUC_{0-24}/Dose, dose normalized area under the curve from 0 to 24 hours; C_{max} /Dose, dose normalized maximum concentration.
Abbreviations: IV, intravenous

17.4.1.2. Pediatric Phase 1 Clinical Trial With Single and Multiple Dose Regimens

Study MK-1986-014

Study MK-1986-014 was a phase 1, two-part, open-label, nonrandomized, multicenter, single and multiple dose study to assess the PK, safety, and tolerability, of tedizolid phosphate in pediatric subjects aged birth (weighing ≥1 kg) to <24 months of age receiving prophylaxis or treatment for a confirmed or suspected infection with gram-positive bacteria and receiving concurrent antibacterial drug treatment with gram-positive antibacterial activity. Subjects were divided into 9 age-and-dosage-based cohorts and administered tedizolid phosphate according to the weight-based doses summarized in Table 35.

The dosages for this study were selected with the objective of achieving plasma exposures (as tedizolid AUC) similar to those observed in adults receiving the therapeutic dose, and were informed by the pharmacokinetic parameters observed in study MK-1986-013 (summarized above).

Table 35. Planned Age Cohorts and Corresponding Tedizolid Phosphate Weight-Based Doses

Part	Group	Cohort	Age Range	Weight based dose (mg/kg)*	Route	Frequency
A	1	1	28 days[a] to <6 months	First 5 subjects (in Group 1): 3.0	IV (1 hour infusion)	Once
		2	6 months to <24 months			
	2	1	Full term[b] neonates from birth to 28 days	All others: BW <10 kg: 3.0		
		2				Twice daily for 3 days
	3	1	Preterm[c] neonates from birth to 28 days	BW 10 to <30 kg: 2.5		Once
		2				Twice daily for 3 days

Part	Group	Cohort	Age Range	Weight based dose (mg/kg)*	Route	Frequency
B	4		28 days[a] to <24 months		Oral	Once
	5		Full term[b] neonates from birth to 28 days			
	6		Preterm[c] neonates from birth to 28 days			

Source: Synopsis Applicant's Report for Study MK-1986-014.
a Preterm or full-term at birth
b Full-term neonate is defined as an infant born ≥37th week of gestation.
c Preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.
*Based on the first IA for these 5 subjects, the dose for the study was kept at 3.0 mg/kg for subjects weighing <10 kg, but adjusted to 2.5 mg/kg for those weighing 10 to <30 kg. Of the 47 allocated subjects, 45 received the 3.0 mg/kg dose and 2 (1 in Group 1 Cohort 2 and 1 in Group 4) received the 2.5 mg/kg dose.
Abbreviations: BW, body weight; IA, interim analysis; IV, intravenous

Of the 49 subjects screened, 47 were enrolled in the study, and received one or more doses of tedizolid phosphate. No subjects discontinued the study. Five subjects identified at the early PK analysis, the first five neonates dosed with IV administration, had 2 or greater of the 3 PK samples below the limit of quantification (BLQ). Citing the biological implausibility, the Applicant replaced these subjects to ensure adequate number of subjects with PK data, per protocol. An additional two neonates with 2 or greater PK samples BLQ were identified after enrollment closure and were not replaced. All enrolled subjects were included in the safety, and PK analysis populations. Patient demographic information for Study MK-1986-014 is shown in Table 46. Both full term and preterm neonates <28 days of age were enrolled in study MK-1986-014, with the youngest participant aged 26 weeks gestational age and weighing 1.05 kg. Overall, tedizolid phosphate appeared to be well tolerated across all cohorts. Protocol deviations were reported for 2 study subjects. One participant in Group 3 Cohort 1 (Single IV dose in preterm neonates age birth to <28 days) received study drug that was not prepared according to the pharmacy manual. One participant in Group 3 Cohort 2 (Multiple IV doses in preterm neonates age birth to <28 days) had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol. The deviations were characterized as not considered to be clinically important, and the subjects' data were included in the safety and PK populations. For additional details on the safety and tolerability of tedizolid phosphate in the clinical trial population, please see Section 10.

The PK analysis population, defined as subjects who received either at least a single IV or oral dose of tedizolid phosphate, and had valid bioanalytical samples collected at protocol specified

time-points, was comprised of all 47 enrolled subjects. By design, subjects were allocated to 1 of 2 sample collection dosage specific schemes, where only 3 post-dose samples were scheduled to be collected from study subjects. The schemes were designed to alternate timepoints between schemes. For Part A single-dose tedizolid phosphate IV dosage, blood samples (0.1 mL of blood per sample) were collected immediately after the end of the 1 hour infusion, and at 3 and 12 hours after the start of infusion in collection scheme 1. In collection scheme 2, samples were collected at 1.5, 6, and 24 hours after the start of infusion. For Part A multiple-dose tedizolid phosphate IV dosage, blood samples (0.1 mL of blood per sample) were collected on Day 3 immediately after the end of the 1 hour infusion (5^{th} dose), and at 3 and 12 hours after the start of infusion for the 5^{th} dose in collection scheme 1. In collection scheme 2, samples were collected on Day 3 at 12 hours after the start of the 4^{th} dose infusion, and 1.5, 6 hours after the start of the 5^{th} dose infusion. For Part B single-dose tedizolid phosphate oral dosage regimen, blood samples (0.1 mL of blood per sample) were collected at 1, 5 and 12 hours post-dose in collection scheme 1. In collection scheme 2, samples were collected at 3, 8, and 24 hours post-dose. PK samples were analyzed using a previously validated bioanalytical method (see Section 17.4.2 for details on in-study method performance). PK data obtained from this study was used to update the existing population PK models for tedizolid phosphate and tedizolid to predict drug exposures in pediatric subjects (See Section 17.4.3).

In the pharmacokinetic population, 40 and 9 subjects had greater than or equal to 2 quantifiable tedizolid and tedizolid phosphate concentrations, respectively. Per protocol PK parameters were only reported for tedizolid. Of the tedizolid PK population, 6/40 subjects were excluded from analysis [3 in Group 2 cohort 2, 1 in Group 3 cohort 2, 1 in Group 4, and 1 in Group 6]. The majority of the exclusions were from subjects with age less than 28 days and the reasons for exclusion were relatively very low and high tedizolid concentrations for 5 and 1 subjects, respectively, when compared to the PK data from the respective age group. The Applicant conducted a comparison of the distribution of demographics for all subjects aged less than 28 days enrolled and those retained in the NCA analysis, and found the demographics were comparable between the two groups with respect to age (after birth), PMA, and weight. Therefore the Applicant concluded that the results of the NCA analysis are considered generalizable across the enrolled neonatal population.

The estimated mean steady state PK parameters for a single oral or IV administration of tedizolid from naïve-pooled noncompartmental analysis are summarized by cohort in Table 36. Mean tedizolid systemic exposures were broadly comparable across age groups after a single IV infusion and after a single oral dose administration. Similar exposures were observed for IV and orally administered tedizolid phosphate, and the absolute bioavailability of the powder for oral suspension formulation was estimated to be 95.2%.

Table 36. Summary of Geometric Mean of Single-Dose Tedizolid PK Parameters Across Cohorts

Group Cohort	Age range (years)	Route and Frequency of Dose*	Number	AUC_{0-24} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	C_{max} (ng/mL)	T_{max}† (h)
1-1/2	28 days[a] to <24 months	IV Once	10	13.6	14.3	2.19	1.33
2-1	Full term[b] neonates from birth to 28 days	IV Once	5 [6 for C_{max}]	8.23	9.21	0.962	1.41
3-1	Preterm[c] neonates from birth to 28 days	IV Once	5 [6 for C_{max}]	15.6	17.8	1.35	1.50
4‡	28 days[a] to <24 months	Oral Once	3	7.92	8.36	1.32	1
5‡	Full term[b] neonates from birth to 28 days	Oral Once	4	9.25	9.44	0.8999	3.03
6‡	Preterm[c] neonates from birth to 28 days	Oral Once	3	14.9	22.1	1.22	8

Source: Reviewer compiled from Tables 11-2, and 11-3 from Applicant's Report for Study MK-1986-014.
* First 5 subjects (in Group 1):3.0 mg/kg. All subsequent subjects (all groups): body weight <10 kg: 3.0 mg/kg, body weight 10 to <30 kg: 2.5 mg/kg.
† Median reported for T_{max}.
‡ Naive pooled PK parameters.
[a] Preterm or full-term at birth.
[b] Full-term neonate is defined as an infant born ≥37th week of gestation.
[c] Preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.
Abbreviations: IV, intravenous; PK, pharmacokinetic

PK data following multiple IV infusions were collected for 7 subjects (4 full-term neonates and 3 preterm neonates) in the study, however following exclusions (summarized above), only PK data for 3 subjects (1 full-term neonate and 2 preterm neonates) was available for analysis.

The estimated mean steady state PK parameters for a multiple IV administration of tedizolid from naïve-pooled noncompartmental analysis are summarized by cohort in Table 37. Mean tedizolid systemic exposures were broadly comparable between full term and preterm neonates after multiple IV infusions, and appear comparable to PK parameters after a single IV infusion administration, suggesting limited accumulation based on twice daily IV infusion administration.

Table 37. Summary of Geometric Mean of Multiple-Dose Tedizolid PK Parameters Across Cohorts

Group Cohort	Age range (years)	Route and Frequency of Dose*	Number	AUC_{0-12} (h*µg/mL)‡	C_{max} (ng/mL)‡	T_{max}† (h)
2-2	Full term[a] neonates from birth to 28 days	IV Twice daily for 3 days	1	10.5	1.82	1.60
3-2	Preterm[b] neonates from birth to 28 days	IV Twice daily for 3 days	2	7.48	1.69	1.08

Source: Reviewer compiled from Tables 14.2-13 and Tables 14.2-16 from Applicant's Report for Study MK-1986-014.
* All groups: body weight <10 kg: 3.0 mg/kg, body weight 10 to <30 kg: 2.5 mg/kg.
† Median reported for T_{max}.
‡ Naive pooled PK parameters.
[a] Full-term neonate is defined as an infant born ≥37th week of gestation.
[b] Preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.
Abbreviations: IV, intravenous; PK, pharmacokinetic

PK data obtained from this study was used to update the existing population PK models for tedizolid to predict drug exposures in pediatric patients (See Section 17.4.3). PK parameters were estimated by linear mixed-effects model performed on natural log-transformed values.

Reviewer comment:

The Applicant's overall findings from this study are consistent with the Reviewer's analysis. We note that the datafile for the bioanalytical results for the pharmacokinetic concentrations (Data source: ADPC.xpt) in this study denoted that three subjects in Cohort 6 received the oral suspension by nasogastric tube, which was not discussed in the clinical study report, and may be a contributing factor to the higher observed median T_{max} for Cohort 6 when compared to the other Cohorts receiving oral suspension. Due to the sparse sampling in this study, individual Bayesian estimates of the PK parameters were also estimated by popPK analysis following development of the pediatric popPK model, and is discussed in more detail in Section 17.4.3.

17.4.1.3. Pediatric Phase 3 Clinical Trial

Study MK-1986-018

Study MK-1986-018 was a Phase 3, randomized, active controlled, parallel-group, multisite, assessor-blinded study to assess the PK, safety, and efficacy of tedizolid phosphate for the treatment of ABSSSI in pediatric patients aged (b) (4) to <12 years of age. Patients were divided into 4 age-based cohorts and administered tedizolid phosphate (IV and/or oral) according to the age, and administered weight-based doses summarized in Table 38; however, no subjects were enrolled with age of less than 28 days.

The dosage regimens selected for this study, informed by the pharmacokinetic parameters observed in study MK-1986-013, and study MK-1986-014, were predicted to achieve plasma exposures (as tedizolid AUC_{0-24}) similar to those observed in adults receiving the therapeutic dose.

Table 38. Planned Age Cohorts and Corresponding Tedizolid Phosphate Weight-Based Doses

Cohort	Age Range	Weight based dose (mg/kg)*
1	6 to <12 years	BW ≥50 kg: 200 mg dose once-daily
2	2 to <6 years	BW ≥30 kg and <50 kg: 2 mg/kg doses every 12 hours
3	28 days to <2 years	
4	Birth to <28 days*	BW 3.2 kg to <30 kg: 2.5 mg/kg doses every 12 hours

Source: Applicant's Synopsis Report for Study MK-1986-018.
* No subjects were enrolled in Cohort 4 [<28 days]
Abbreviations: BW, body weight

Of the 101 subjects screened, 100 were enrolled in the study, randomized, and received one or more doses of tedizolid phosphate (n=75) or protocol specified comparator (n=25). Note that no subjects were enrolled for Cohort 4, subjects aged <28 days. Four (5.3%) and two (8.0%) subjects discontinued from both the study intervention and the study in the tedizolid phosphate and comparator arms, respectively. All 100 enrolled subjects (75 tedizolid phosphate, 25 comparator) were included in the intent to treat (ITT) population, and safety populations. Patient demographic information for Study MK-1986-018 is shown in Table 46. The CE-TOC population consisted of 91 patients (68 tedizolid phosphate, 23 comparator) from the ITT population with an ABSSSI clinical diagnosis caused by a suspected or confirmed gram-positive pathogen (baseline Gram stain or culture), who received a sufficient course of therapy (at least 48 hours of dosing with study drug) and had no concomitant systemic antibacterial drug therapy from the first infusion of study drug through the test of cure (TOC) Visit that is potentially effective against baseline pathogen except adjunctive aztreonam and/or metronidazole in subjects with wound infections, and who completed the EOT, and TOC Investigator's assessments (unless assessed as failures at any timepoint before the TOC Visit). The MITT population consisted of 60 patients (46 tedizolid phosphate, 14 comparator) from the ITT population with an ABSSSI caused by a confirmed gram-positive pathogen isolated from the baseline culture (baseline culture collected from 54 tedizolid phosphate patients, and 17 comparator patients). The ME population consisted of 59 patients (45 tedizolid phosphate, 14 comparator) from the MITT who were also in the CE-TOC. The pharmacokinetic population consisted of 74 patients in the tedizolid phosphate arm.

Overall, tedizolid phosphate appeared to be well tolerated across all cohorts. Important protocol deviations occurred in 34 subjects, 2 of which were considered clinically significant. Both subjects with clinically significant protocol deviations were in the tedizolid phosphate arm. One subject had received study drug that was expired or damaged. One subject missed safety

laboratory assessments (entire panel of either chemistry or hematology or both) from Visit 1, or both Visit 4 or 6. No subject data were excluded due to protocol deviations and these deviations do not appear to affect the overall clinical pharmacology conclusions being drawn from the study. For additional details on the safety and tolerability of tedizolid phosphate in the clinical trial population, please see Section 10.

The PK analysis population, defined as subjects who received either at least a single IV or oral dose of tedizolid phosphate, and had valid bioanalytical samples collected at protocol specified time-points, was comprised of 74 of the 75 subjects in the tedizolid phosphate arm. Quantifiable tedizolid phosphate and tedizolid plasma concentrations were obtained from 50 and 73 patients, respectively. The schedule for PK sample collection (0.5 mL of blood per sample) was route specific as follows: (1) if the first dose was IV, at Visit 2 between 5 to 80 minutes after the end of the 1 hour infusion and between 4 to 12 hours post-infusion, at Visit 3 predose and between 4 to 12 hours post-infusion, and anytime during Visit 4; (2) if the first dose was oral suspension, at Visit 2 between 4 to 12 hours post-dose, at Visit 3 predose and between 4 to 12 hours post-dose, and anytime during Visit 4.

PK samples were analyzed using a previously validated bioanalytical method (see Section 17.4.2 for details on in-study method performance). PK data obtained from this study was used to update the existing popPK models for tedizolid phosphate and tedizolid to predict drug exposures in pediatric patients aged birth to <12 years. PK parameters were estimated by linear mixed-effects model performed on natural log-transformed values shown in Table 39, which are reported in the popPK report discussed in the Pharmacometric review in Section 17.4.3. As noted in the popPK report, all PK observations were below the lower limit of quantification concentrations for 1 participant, hence that subjects data were excluded from analysis.

Table 39. Summary of Geometric Least Squares Mean (%CV) of Tedizolid PK Parameters

First dose formulation (Number)	First dose AUC_{0-24} (hr*µg/mL)	First dose C_{max} (µg/mL)	First dose C_{12h} (µg/mL)	Last dose formulation (Number)	Steady-state AUC_{0-24} (hr*µg/mL)	Steady-state C_{max} (µg/mL)	Steady-state C_{12h} (µg/mL)
IV infusion (n=58)	24.01 (23.34)	2.23 (25.96)	0.39 (47.97)	IV infusion (n=24)	34.18 (37.26)	3.00 (29.48)	0.59 (71.81)
Oral suspension (n=15)	16.02 (25.27)	1.08 (25.86)	0.29 (56.09)	Oral suspension (n=49)	25.45 (32.51)	1.58 (27.15)	0.51 (58.93)

Source: Reviewer compiled from Tables 20, 21, 26, and 27 from Applicant's from popPK report.
Abbreviations: CV, Coefficient of variation; PK, pharmacokinetic; IV, intravenous

Blinded investigator assessment of the clinical response as clinical success, failure, or indeterminate based on protocol-specified criteria was determined as a secondary outcome of the study. Note that this outcome was not powered for an efficacy analysis, and descriptive statistics were used to describe the data. The clinical success at EOT and TOC visit (22 to 29 days

after first dose) were evaluated for tedizolid and comparator arms in study MK-1986-018 as shown in Table 40. Greater than 90% clinical success was observed at both timepoints evaluated for both tedizolid and the comparator product administered.

Table 40. Summary of Blinded Investigators Assessment of Clinical Response in Intent-to-Treat Population

	Tedizolid			Comparator			Estimated	
Clinical Response	n	(%)	95% CI[a]	n	(%)	95% CI[a]	Difference (%)[b]	95% CI[b]
Clinical Response (EOT)								
Number of Participants	75			25				
Clinical Success	71	(94.7)	(86.9, 98.5)	25	(100.0)	(86.3, 100.0)	-5.3	(-10.4, -0.2)
Clinical Failure or Indeterminate	4	(5.3)		0	(0.0)			
Clinical Failure	0	(0.0)		0	(0.0)			
Indeterminate	4	(5.3)		0	(0.0)			
Clinical Response (TOC)								
Number of Participants	75			25				
Clinical Success	70	(93.3)	(85.1, 97.8)	23	(92.0)	(74.0, 99.0)	1.3	(-10.7, 13.4)
Clinical Failure or Indeterminate	5	(6.7)		2	(8.0)			
Clinical Failure	0	(0.0)		0	(0.0)			
Indeterminate	5	(6.7)		2	(8.0)			

[a]An exact two-sided 95% CI determined for the rate of clinical success in each treatment group using the Clopper-Pearson method.
[b]The estimated difference (Tedizolid minus Comparator group) in the clinical success rate and 95% confidence interval calculated using the unstratified method of Miettinen and Nurminen.
EOT = End of Therapy; TOC = Test of Cure.

Source: Table 14.2-1 Applicant's Report for Study MK-1986-018.

Reviewer comment:

The Applicant's overall findings from this study are consistent with the Reviewer's analysis. PopPK was used to estimate the expected exposures in subjects from this study. See Section 17.4.3 for additional details.

17.4.2. Summary of Bioanalytical Method Validation and Performance

Bioanalytical methods were developed and validated to support the quantification of tedizolid phosphate (prodrug) and tedizolid (active moiety) in samples generated from clinical studies. Details regarding validated ultra-performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS) assays for quantification of tedizolid phosphate and tedizolid in plasma are summarized in Table 41 and Table 42 below. These details on bioanalytical method performance were reviewed and are acceptable.

Table 41. Bioanalytical Method Validation Summary

Validation report #	157097ANUI Revision 02 (23-NOV-2023)	
Analytes	Tedizolid Phosphate (MK-1986), and tedizolid	
CRO	(b) (4)	
Method of Detection	UPLC-MS/MS	
Biological Matrix	Human plasma	
Anticoagulant	Ethylenediaminetetraacetic acid (EDTA) dipotassium (K_2) and EDTA tripotassium (K_3)	
Extraction Method	Protein precipitation extraction technique	
Internal Standard(s)	MK-1986-^{13}C-d3 and tedizolid-^{13}C-d3	
Analyte	MK1986	Tedizolid
Calibration Standard Range (ng/mL)	5 to 1000	5 to 1000
Calibration Inter-day Accuracy (%RE)	-2 to 5	-3 to 4
Calibration Inter-day Precision (%CV)	≤7	≤6
QC Range (ng/mL)	5.00, 15.00, 500.00, 750.00	5.00, 15.00, 500.00, 750.00
Highest Dilution QC (ng/mL)	40005.71	172,600.00
QC Inter-day Accuracy (%RE)	-5 to 1	-5 to 3
QC Inter-day Precision (%CV)	≤5	≤5
QC Intra-day Accuracy (%RE)	-5 to 2	-4 to 3
QC Intra-day Precision (%CV)	≤4	≤5
Long-Term Stability Analytes in Matrix	1406 days at -20°C and 606 days at -80°C	
Long-Term Stability Analytes & Internal Standard in Solution at Low and High Concentration	278 days at 4°C	

Source: Generated by the FDA review team; Adapted from (b) (4) bioanalytical report project number 157097ANUI.
Abbreviations: RE, relative error; CV, coefficient of variation; CRO, contract research organization; QC, quality control; UPLC-MS/MS, ultra-performance liquid chromatography with tandem mass spectrometry

Table 42. Bioanalytical Method Performance Summary

Clinical Study Number	**MK-1986-013**		**MK-1986-014**		**MK-1986-018**	
Samples Received	A total of 217 of the 369 samples received were analyzed. The bioanalytical performance report noted that some blood samples had designations of split 1 or split 2 and, that samples which were not analyzed were split 2 samples. The storage temperature was -20°C and all samples were analyzed within the established stability period.		All 141 of the samples received were analyzed. The storage temperature was -20°C and all samples were analyzed within the established stability period.		A total of 340 of the 376 samples received were analyzed. CRO notes that the 36 samples not analyzed were either coded as a second aliquot of a sample (12), unacceptable for analysis (22), or not analyzed as per Sponsor's request (2). The storage temperature was -20°C and all samples were analyzed within the established stability period.	
CRO	(b) (4)		(b) (4)		(b) (4)	
Method of Detection	UPLC-MS/MS					
Biological Matrix	Human plasma					
Anticoagulant	EDTA K_2		EDTA K_3		EDTA K_3	
	MK-1986	Tedizolid	MK-1986	Tedizolid	MK-1986	Tedizolid
Calibration Standard Inter-run Accuracy (RE%)	-2 to 1	-3 to 2	-1 to 2	-2 to 3	-2 to 1	-1 to 1
Calibration Standard Inter-run Precision (%CV)	≤4	≤3	≤5	≤6	≤5	≤3
QC Range/Levels (ng/mL)	15.00 to 750.00					
QC Inter-run Accuracy (%RE)	-2 to 2	-2 to 1	-1 to 5	-2 to 6	-10 to 5	-11 to 7
QC Inter-run Precision (%CV)	≤5	≤6	≤8	≤15	≤19 LOQ, ≤7	≤20 LOQ, ≤17
Method Reproducibility Incurred Sample Reanalysis (Percentage within ± 20%)	100% (n=19)	96% (n=50)	95% (n=44)	96% (n=51)	94% (n=35)	91% (n=45)

Clinical Study Number	MK-1986-013		MK-1986-014		MK-1986-018	
Sample Chromatograms provided ?	Yes	Yes	Yes	Yes	Yes	Yes

Source: Generated by the FDA review team; Adapted from 2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES Appendix 2.7.2-absssichild: 3, and individual bioanalytical reports (b) (4) report 160394APVK, and (b) (4) reports 190099AVCC, and 190093AVBT.
Abbreviations: RE, relative error; CV, coefficient of variation; CRO, contract research organization; QC, quality control; EDTA, Ethylenediaminetetraacetic acid; UPLC-MS/MS, ultra-performance liquid chromatography with tandem mass spectrometry

Reviewer comment:

Because MK-1986 and Tedizolid PK data from Studies MK-1986-013, MK-1986-014, and MK-1986-018 provide key supportive information for the proposed dosage regimens in pediatric patients from (b) (4) up to less than 12 years of age, an Office of Study Integrity and Surveillance (OSIS) bioanalytical site inspection was requested (June 20, 2024). OSIS determined that an inspection was not needed (See OSIS memorandum dated August 5, 2024) and noted the rationale as OSIS conducted a Remote Regulatory Assessment for the analytical site in (b) (4) and concluded that data from the reviewed studies were reliable. The submitted bioanalytical method validation and performance reports are acceptable from a clinical pharmacology perspective.

17.4.3. Pharmacometrics

The primary objectives of the Applicant's analysis were to:

- Develop a pediatric popPK model for tedizolid, based on a previously developed structural PK model in adolescents/adults and newly added pediatric PK data in subjects from birth to <12 years of age to characterize tedizolid PK in pediatric patients (study MK-1986-018);
- Characterize the effect of intrinsic factors, such as age, race, sex, estimated glomerular filtration rate (eGFR), and total bilirubin, on the PK variability of tedizolid;
- Derive individual tedizolid exposure estimates and predict steady-state exposures in pediatric subjects, to support comparisons of exposures with adults and adolescents and dosing recommendations;
- Perform a PTA analysis in pediatric subjects with ABSSSI from birth to <18 years of age;
- Conduct exploratory graphical analyses to explore potential relationships between tedizolid exposures and selected efficacy endpoints in pediatric subjects with ABSSSI from Study MK-1986-018.

The Applicant's final pediatric popPK model adequately described the observed tedizolid plasma concentrations in pediatric subjects from birth (gestational age ≥26 weeks and weighing ≥1 kg) to <18 years of age. The developed popPK model was found suitable for performing simulations and predicting tedizolid exposure metrics under the proposed weight-band dosage. The predicted pediatric tedizolid exposures were relied upon for the purpose of exposure comparison to adults and adolescents, and thereby provided support for the extrapolation of efficacy and supported safety of the proposed pediatric dosage. The popPK model was used to support the current submission for commercially available SIVEXTRO oral and IV formulations, as outlined in Table 43.

The final pediatric popPK model identified body weight as the only significant and clinically meaningful covariate on the PK of tedizolid. Parameter estimates for the final model were estimated with acceptable precision. The goodness-of-fit (GOF) plots showed a good agreement between the observed and the individual predicted concentrations without any obvious bias over time. The visual predictive check (VPC) plots stratified both by age and weight showed a good agreement between the observed and the simulated concentrations.

Table 43. Specific Comments on Applicant's Final PopPK Model

Utility of the final model		Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic, extrinsic factors, and the proposed dosage	The final recommended pediatric weigh-band dosage for patients from (b) (4) (≥26 weeks gestational age and weighing ≥1 kg) to <18 years of age is predicted to result in tedizolid systemic exposure (steady-state AUC_{0-24}) similar to that in adult patients given tedizolid phosphate 200 mg once daily by either intravenous infusion or oral tablet.	The statement is acceptable. The final pediatric popPK model retained body weight as the only covariate on clearances and volumes of distribution terms. The Applicant's final model is acceptable for generating exposure estimates for pediatric extrapolation and exposure matching. The final recommended pediatric weight-band dosage was deemed acceptable, and was predicted to result in tedizolid exposures that appear to be safe and efficacious. However, the initial pediatric weight-band dosage proposed by the Applicant for patients weighing 1 to <2 kg (b) (4) and not acceptable, due to a lack of safety data for this exposure in this pediatric population. The dosage was ultimately revised to 3 mg/kg for patients with body weight 1 to <2 kg, see further discussion in Sections 6.2.1 and 17.4.3.2.2

Utility of the final model		Reviewer's Comments
Derive post-hoc exposure metrics for exposure- response analyses	The Applicant perform a graphical assessment of the relationship between the model-derived AUC_{0-24} and clinical response (success, failure, or indeterminate) at the test of cure visit (22 to 29 days after first dose).	The exploratory exposure-response plot suggested the absence of an exposure-clinical efficacy relationship.

Source: Reviewer analysis
Abbreviations:; AUC_{0-24},area under the curve over 24 hours; PopPK, population pharmacokinetic

Population Pharmacokinetic Analysis

A popPK model was previously developed in the adult/adolescent population with rich PK sampling schemes (refer to the Clinical Pharmacology and Biopharmaceutics Reviews for NDA 205436 IV and NDA 205435 oral tablet products). The current updated popPK model (referred to as pediatric popPK model throughout the section) was refined from the previous popPK model using pooled PK data from subjects ages birth to 18 years of age, after oral (suspension formulation) and/or IV administration of single or repeated doses of tedizolid phosphate. Due to the rapid conversion *in vivo* of the tedizolid phosphate to the active moiety tedizolid, the popPK model only included tedizolid plasma concentrations data in model development.

17.4.3.1. Model Development

Data

Newly collected pediatric PK data were pooled with historical adult/adolescent PK data, and the previously developed popPK model was updated to describe the PK of tedizolid from three Phase 1 pediatric studies (MK-1986-026, MK-1986-013, and MK-1986-014), and two Phase 3 studies (MK-1986-012 and MK-1986-018), shown in Table 44.

The historical adult/adolescent PK dataset already contained data from Studies MK-1986-026 (146 tedizolid concentrations in 20 subjects, 11 to 17 years of age), MK-1986-012 (412 tedizolid concentrations in 89 subjects, 12 to 18 years of age), and MK-1986-013 (153 tedizolid concentrations in 21 subjects, 2 to <12 years old), which were used in the previous adult/adolescent popPK model.

Tedizolid concentrations BLQ of 5 ng/mL represented 5% of all observations and were excluded from analysis for all participants. PK samples with outlier concentrations, missing concentrations or missing collection times were removed from the final PK dataset for analysis.

Following exclusions, a total of 249 subjects providing 1191 concentrations values from the five clinical studies were retained in the pediatric analysis dataset: 213 (18%) from study MK-1986-013, 99 (8%) from study MK-1986-014, 321 (27%) from study MK-1986-018, 412 (35%) from study MK-1986-012, and 146 (12%) from study MK-1986-026. Following exclusions, 30

observations (3%) were retained from 6 adult patients aged 18-years-old, all from study MK-1986-012.

Data disposition for tedizolid is summarized in Table 45. Characteristics of subjects in all five studies, including covariates of interest, are summarized in Table 46.

Table 44. Summary of Designs of Studies Included in the Population PK Analyses

Study	Design	Treatment Regimen	PK Sampling	PK population (n)
Phase 1 studies				
MK-1986-026 (P026MK1986, P026, TR701-111)	Open-label, multicenter, two-part, single-dose, parallel-design, safety, and PK study of oral and IV tedizolid phosphate	Part A: single dose 200 mg tedizolid phosphate oral tablet under fasted conditions Part B: single dose 200 mg tedizolid phosphate IV infusion	Part A: predose and 1, 2, 4, 6, 8, 12, and 24 hours postdose Part B: predose and 0.5 hours (during infusion), 1 hour (at end of infusion), and 1.5, 2, 4, 6, 12, and 24 hours after start infusion	Patients receiving prophylaxis for a confirmed or suspected infection with gram-positive bacteria, age 12 to 17 years (n = 20, 16 male, 4 female, weight range 38.5 to 83.1 kg) Part A: n = 10 Part B: n = 10
MK-1986-013 (P013MK1986, P013, TR701-120)	Open-label, multicenter, two-part, single-dose safety and PK study of oral and IV tedizolid phosphate	Part A: tedizolid phosphate IV infusion Group 1 Cohort 1: 5 mg/kg Cohort 2: 4 mg/kg Group 2 Cohort 1: 6 mg/kg Cohort 2: 3 mg/kg Part B: tedizolid phosphate oral suspension	Part A: Group 1: 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; Group 2: immediately after the end of the 1 hour infusion and at 3, 6, 12, 24, and 48 hours after the start of infusion	Hospitalized patients receiving prophylaxis for a confirmed or suspected infection with gram-positive bacteria, age 2 to <12 years (n = 32, 19 male, 13 female, weight range 12.6 to 42.3 kg) Group 1: 6 to <12 years (n = 10; n = 5 for each cohort)

Study	Design	Treatment Regimen	PK Sampling	PK population (n)
			Part B: Group 3: 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose; Group 4: 3, 6, 9, 12, 24, and 48 hours postdose	Group 2: 2 to <6 years (n = 10; n = 5 for each cohort) Group 3: 6 to <12 years (n = 6) Group 4: 2 to <6 years (n = 6)
		Group 3: 4 mg/kg Group 4: 3 mg/kg		
MK-1986-014 (P014MK1986, P014, TR701-121)	Open-label, multicenter, two-part, single-dose safety and PK study of oral and IV tedizolid phosphate	Part A: tedizolid phosphate IV infusion Part B: tedizolid phosphate oral suspension First 5 subjects in Group 1: 3 mg/kg; All subsequent subjects (all groups): BW <10 kg: 3 mg/kg BW 10 to <30 kg: 2.5 mg/kg	Subjects randomized to 1 of 2 collection schemes for each part of the study Part A: Scheme 1: immediately after the end of the 1 hour infusion and 3 and 12 hours after the start of infusion Scheme 2: 1.5, 6, and 24 hours after the start of infusion Part B: Scheme 1: 1, 5, and 12 hours postdose Scheme 2: at 3, 8, and 24 hours postdose	Hospitalized patients receiving prophylaxis for a confirmed or suspected infection with gram-positive bacteria, age birth to <2 years (n = 47, 29 male, 18 female, weight range 1.05 to 14 kg) Age 28 days to <2 years: Group 1 (IV, n = 10) and Group 4 (oral, n = 4) Age <28 days: • Full-term neonates Group 2 (IV, n = 12) and Group 5 (oral, n = 4) • Preterm neonates Group 3 (IV, n = 13) and Group 6 (oral, n = 4;

Study	Design	Treatment Regimen	PK Sampling	PK population (n)
				n = 3 of 4 via a nasogastric tube) • Preterm and full-term neonates (n = 8) received multiple-dose IV infusion BID for up to 3 days.
Phase 3 studies				
MK-1986-012 (P012MK1986, P012, TR701-122)	Randomized (3:1 ratio), active controlled, single-blind, multicenter, global Phase 3 study to assess the safety and efficacy of intravenous (IV) and/or oral tedizolid phosphate 200 mg once daily for 6 days versus that of IV and/or oral protocol-specified active comparators for 10 days, for the treatment of ABSSSI in subjects aged 12 to <18 years.	IV infusion and/or oral tablet 200 mg tedizolid phosphate, QD, for 6 days A minimum 24 hour period of IV therapy before the Investigator assessed for a switch from IV to oral therapy. OR Comparator for 10 days.	Day 1: IV dose: a sample between 5 to 80 minutes and a sample between 4 and 12 hours after IV infusion; oral dose: 2 samples between 4 to 12 hours postdose at least 60 minutes apart 48- to 72-hour visit: (regardless of route of dosing) a sample within 60 minutes prior to dosing and a sample between 4 and 12 hours after dosing Day 7: Collect 1 blood sample at any time	Patients with ABSSSI, age 12 to <18 years (n = 120, 75 male, 45 female, weight range 28 to 126 kg) n = 91 were enrolled and treated with tedizolid phosphate: n = 88 (96.7%) of tedizolid phosphate arm completed the trial; n = 3 (3.3%) of tedizolid phosphate arm discontinued both study treatment and the trial; n = 89 in tedizolid phosphate arm included in popPK analysis

Study	Design	Treatment Regimen	PK Sampling	PK population (n)
MK-1986-018 (P018MK1986, P018, TR701-128)	Randomized (3:1 ratio), active controlled, parallel-group, multisite, assessor blinded Phase 3 study to assess the safety and efficacy of tedizolid phosphate (IV and/or oral) versus protocol-specified active comparators (IV and/or oral) for the treatment of ABSSSI in subjects aged birth to < 12 years with ABSSSI.	BW ≥50 kg: IV infusion and/or oral suspension 200 mg tedizolid phosphate, QD, for 6 days. BW ≥30 kg and <50 kg: IV infusion and/or oral suspension 2 mg/kg tedizolid phosphate, BID, for 6 days. BW 3.2 kg to <30 kg IV infusion and/or oral suspension 2.5 mg/kg tedizolid phosphate, BID, for 6 days OR Comparator for 10 days.	For Cohorts 1, 2, and 3: Day 1 IV: a sample between 5 and 80 minutes and a sample between 4 and 8 hours if BID dosing or 4 to 12 hours if QD dosing Day 1 oral: 2 samples between 4 and 12 hours postdose at least 90 minutes apart Visit 3: (regardless of route): a predose sample within 1 hour prior dosing and a sample between 4 and 8 hours after dosing (either dose if BID). Visit 4: Collect 1 blood sample at any time.	Patients aged 28 days to <12 years with ABSSSI (n=100, 53 male, 47 female, weight range 6.0 to 68.0 kg) n = 75 were enrolled and treated with tedizolid phosphate: n = 71 (94.7%) of tedizolid phosphate arm completed the trial; n = 4 (5.3%) of tedizolid phosphate arm discontinued both study treatment and the trial; n = 73 in tedizolid phosphate arm included in popPK analysis

Source: Reviewer compiled from popPK report Table 1
Note: Reported n's for Study MK-1986-014 represent enrolled subjects; a total of 12 subjects were excluded from the popPK analysis due to either all BLQ concentrations (n = 6), analyst-identified outliers (n = 2), or extremely low outlying observed concentration-time profiles (n = 4).
Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; BID, twice daily; BW, body weight; BLQ, below the limit of quantitation; IV, intravenous; n, number of subjects; QD, once daily; PK, pharmacokinetic; popPK, population pharmacokinetic.

Table 45. Summary of Tedizolid Pharmacokinetic Data Disposition for Pediatric Studies Included in the Modeling Dataset

Description	P012	P013	P014	P018	P026	Total
Total subjects dosed with tedizolid phosphate	91	32	47	75	20	265
Number included	89	32	35	73	20	249
Total number of tedizolid phosphate doses	535	32	87	1190	20	1864
Number included	517	32	47	717	20	1333
Total tedizolid PK observations	430	217	115	327	147	1236
Number included	412	213	99	321	146	1191
Number of tedizolid PK BLQ	8	0	23	5	20	56

Source: Reviewer compiled from popPK dataset.
Abbreviations: BLQ, below limit of quantitation; PK, pharmacokinetic

Table 46. Summary of Demographic Characteristics and Laboratory Values for Subjects in Pediatric Studies Included in the Modeling Dataset

Variable	Statistic	Study					Overall
		MK-1986-013	MK-1986-014	MK-1986-018	MK-1986-026	MK-1986-012	
Baseline Age (y)	Mean (SD)	5.781 (2.624)	0.273 (0.453)	5.874 (3.626)	14.350 (1.694)	14.966 (1.755)	9.006 (6.005)
	Median	5.500	0.052	7.000	14.000	15.000	9.000
	Min, Max	2.00, 11.00	0.00, 1.60	0.33, 11.00	11.00, 17.00	12.00, 18.00	0.00, 18.00
	N	32	35	73	20	89	249
Baseline Body Weight (kg)	Mean (SD)	22.49 (8.94)	4.60 (3.08)	23.88 (12.83)	60.10 (12.64)	59.61 (17.51)	36.67 (25.15)
	Median	21.25	3.43	22.00	63.45	56.20	34.00
	Min, Max	12.6, 42.3	1.0, 11.0	6.0, 59.0	38.5, 83.1	27.6, 126.3	1.0, 126.3
	N	32	35	73	20	89	249
Baseline BMI (kg/m^2)	Mean (SD)	15.95 (2.00)	13.51 (3.29)	17.72 (3.63)	21.94 (3.41)	21.96 (4.87)	18.76 (4.98)
	Median	15.42	12.73	17.36	22.50	21.20	18.31
	Min, Max	12.7, 21.0	9.1, 21.5	10.7, 27.0	16.0, 28.4	14.2, 45.0	9.1, 45.0
	N	32	35	73	20	89	249
Baseline BSA (m^2)	Mean (SD)	0.849 (0.242)	0.260 (0.122)	0.853 (0.324)	1.653 (0.214)	1.634 (0.275)	1.113 (0.568)
	Median	0.805	0.213	0.857	1.730	1.577	1.144
	Min, Max	0.54, 1.35	0.10, 0.54	0.29, 1.57	1.25, 2.01	1.01, 2.42	0.10, 2.42
	N	32	35	73	20	89	249
IBW (kg)	Mean (SD)	23.17 (8.45)	5.38 (3.17)	22.19 (9.79)	44.97 (4.91)	45.26 (7.32)	30.03 (16.44)
	Median	20.20	4.29	25.37	45.19	43.84	32.80
	Min, Max	11.0, 41.5	1.9, 16.5	4.3, 39.1	34.7, 52.3	29.2, 71.8	1.9, 71.8
	N	32	35	73	20	89	249
Baseline Height (cm)	Mean (SD)	116.70 (20.96)	55.19 (14.88)	112.68 (27.66)	164.84 (9.14)	163.48 (10.72)	127.46 (41.82)
	Median	110.50	51.00	124.00	165.50	163.00	141.00
	Min, Max	81.8, 158.5	34.0, 100.0	51.0, 154.0	145.0, 178.0	133.0, 193.0	34.0, 193.0
	N	32	35	73	20	89	249
Baseline Total Bilirubin (mg/dL)	Mean (SD)	0.31 (0.28)	5.22 (6.36)	0.42 (0.27)	0.60 (0.26)	0.61 (0.37)	1.16 (2.89)
	Median	0.21	2.98	0.30	0.60	0.50	0.44
	Min, Max	0.1, 1.4	0.1, 30.0	0.1, 1.1	0.2, 1.0	0.2, 2.2	0.1, 30.0
	N	32	35	73	20	89	249
Baseline eGFR (Bedside Schwartz Equation) ($mL/min/1.73\ m^2$)	Mean (SD)	137.31 (37.28)	70.41 (51.82)	102.44 (28.47)	104.23 (18.92)	101.78 (17.93)	102.33 (34.94)
	Median	133.76	40.70	103.79	101.04	99.28	102.50
	Min, Max	89.6, 231.4	17.4, 201.9	31.4, 195.7	69.7, 156.8	59.6, 145.8	17.4, 231.4
	N	32	35	73	20	89	249
Baseline eGFR (Schwartz Equation) ($mL/min/1.73\ m^2$)	Mean (SD)	184.19 (50.01)	80.99 (61.66)	132.43 (38.86)	104.23 (18.92)	152.32 (38.54)	136.70 (52.29)
	Median	179.43	54.60	133.45	101.04	145.08	137.06
	Min, Max	120.2, 310.4	19.1, 224.5	42.2, 262.5	69.7, 156.8	87.9, 295.1	19.1, 310.4
	N	32	35	73	20	89	249
Gestational Age (weeks)	Mean (SD)	NA	36.87 (3.66)	NA	NA	NA	36.87 (3.66)
	Median	NA	38.00	NA	NA	NA	38.00
	Min, Max	NA	26.6, 41.0	NA	NA	NA	26.6, 41.0
	N	NA	35	NA	NA	NA	35
Postmenstrual Age (months)	Mean (SD)	NA	11.75 (5.85)	NA	NA	NA	11.75 (5.85)
	Median	NA	9.30	NA	NA	NA	9.30
	Min, Max	NA	6.6, 28.2	NA	NA	NA	6.6, 28.2
	N	NA	35	NA	NA	NA	35
Sex, N (%)	Male	19 (59.4)	23 (65.7)	38 (52.1)	16 (80)	56 (62.9)	152 (61)
	Female	13 (40.6)	12 (34.3)	35 (47.9)	4 (20)	33 (37.1)	97 (39)
Race, N (%)	White	26 (81.2)	24 (68.6)	56 (76.7)	17 (85)	78 (87.6)	201 (80.7)
	Asian	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	1 (0.4)
	Black or African American	4 (12.5)	1 (2.9)	10 (13.7)	1 (5)	11 (12.4)	27 (10.8)
	Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	American Indian/Alaska Native	0 (0)	0 (0)	1 (1.4)	0 (0)	0 (0)	1 (0.4)
	Multiple or other	2 (6.2)	10 (28.6)	6 (8.2)	1 (5)	0 (0)	19 (7.6)

Variable	Statistic	Study					Overall
		MK-1986-013	MK-1986-014	MK-1986-018	MK-1986-026	MK-1986-012	
Geographical Region, N (%)	Missing	0 (0)	0 (0)	0 (0)	20 (100)	89 (100)	109 (43.8)
	Europe	10 (31.2)	21 (60)	51 (69.9)	0 (0)	0 (0)	82 (32.9)
	South Africa	0 (0)	0 (0)	10 (13.7)	0 (0)	0 (0)	10 (4)
	North America/ Latin America/ Australia/New Zealand	22 (68.8)	14 (40)	12 (16.4)	0 (0)	0 (0)	48 (19.3)
Dose Group, N (%)	2 mg/kg	0 (0)	0 (0)	19 (26)	0 (0)	0 (0)	19 (7.6)
	2.5 mg/kg	0 (0)	2 (5.7)	49 (67.1)	0 (0)	0 (0)	51 (20.5)
	3 mg/kg	11 (34.4)	33 (94.3)	0 (0)	0 (0)	0 (0)	44 (17.7)
	4 mg/kg	11 (34.4)	0 (0)	0 (0)	0 (0)	0 (0)	11 (4.4)
	5 mg/kg	5 (15.6)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2)
	6 mg/kg	5 (15.6)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2)
	200 mg	0 (0)	0 (0)	5 (6.8)	20 (100)	89 (100)	114 (45.8)

Source: Excerpt popPK report Table 4 (Schwartz and Furth 2007; Schwartz et al. 2009)
Abbreviations: BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; IBW, ideal body weight; Max, maximum; Min, minimum; N, number of participants; NA, not applicable

Previous adult/adolescent popPK model

A popPK model for tedizolid was previously developed for the adult/adolescent population in the original NDA submissions. Briefly, tedizolid PK was best described by a two-compartment model with linear first-order elimination, and a delayed absorption for the oral tablet (with a zero-order 'release' of drug from the tablet within the gastrointestinal tract with lag time, and first-order absorption). Interindividual variability (IIV) was included on clearance (CL), central volume of distribution (Vc), and the absorption rate constant (ka). Residual variability (RV) was tested as a log-additive error model (additive error model using logarithmically transformed concentrations).

Ideal body weight and total bilirubin were found to be statistically significant covariates for CL and ideal body weight was found to be a statistically significant covariate on Vc. The structural popPK model for the adult/adolescent population served as the initial step for the pediatric popPK model.

Pediatric Base model

The base model was described by a two-compartment model with linear first-order elimination, a zero-order input of the drug into the GI tract without lag time for the oral tablet, and a first-order absorption from the GI tract into the systemic circulation

for the oral tablet and suspension. Separate bioavailability parameters were estimated for the oral tablet (TABF1) and for the oral suspension (SUSPF1).

The IIV was modelled assuming a log-normal distribution for patient level random effects. The IIV was included on the duration of the zero-order input for tablet (D1), ka, CL, and Vc parameters, using exponential error models.

The RV was included as a log-additive error model on the dependent variable, with separate RV terms estimated for the Phase 1 IV data and the Phase 1 oral plus Phase 3 data.

Pediatric Covariate analysis

The covariates that were investigated in the updated pediatric popPK model included (b) (4) baseline body weight (kg), baseline (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) Therefore, both covariates were not retained in the final pediatric popPK model. (b) (4)

The final pediatric popPK model only retained body weight as a covariate on clearance-related and volume-related parameters.

Pediatric Final model

The parameter estimates for the final pediatric popPK model are listed in Table 47. The popPK model parameters were estimated with acceptable precision with relative standard error (RSE) <5% for CL and Vc and RSE <29% for all PK parameters. The IIV for CL was estimated with low shrinkage of 16% and high shrinkage (>30%) for Vc, D1 and ka.

The GOF plots for the final covariate model are shown in Figure 5. Prediction-corrected VPC (pcVPC) plots by age categories and pcVPC by weight quartiles were shown in Figure 6 and Figure 7.

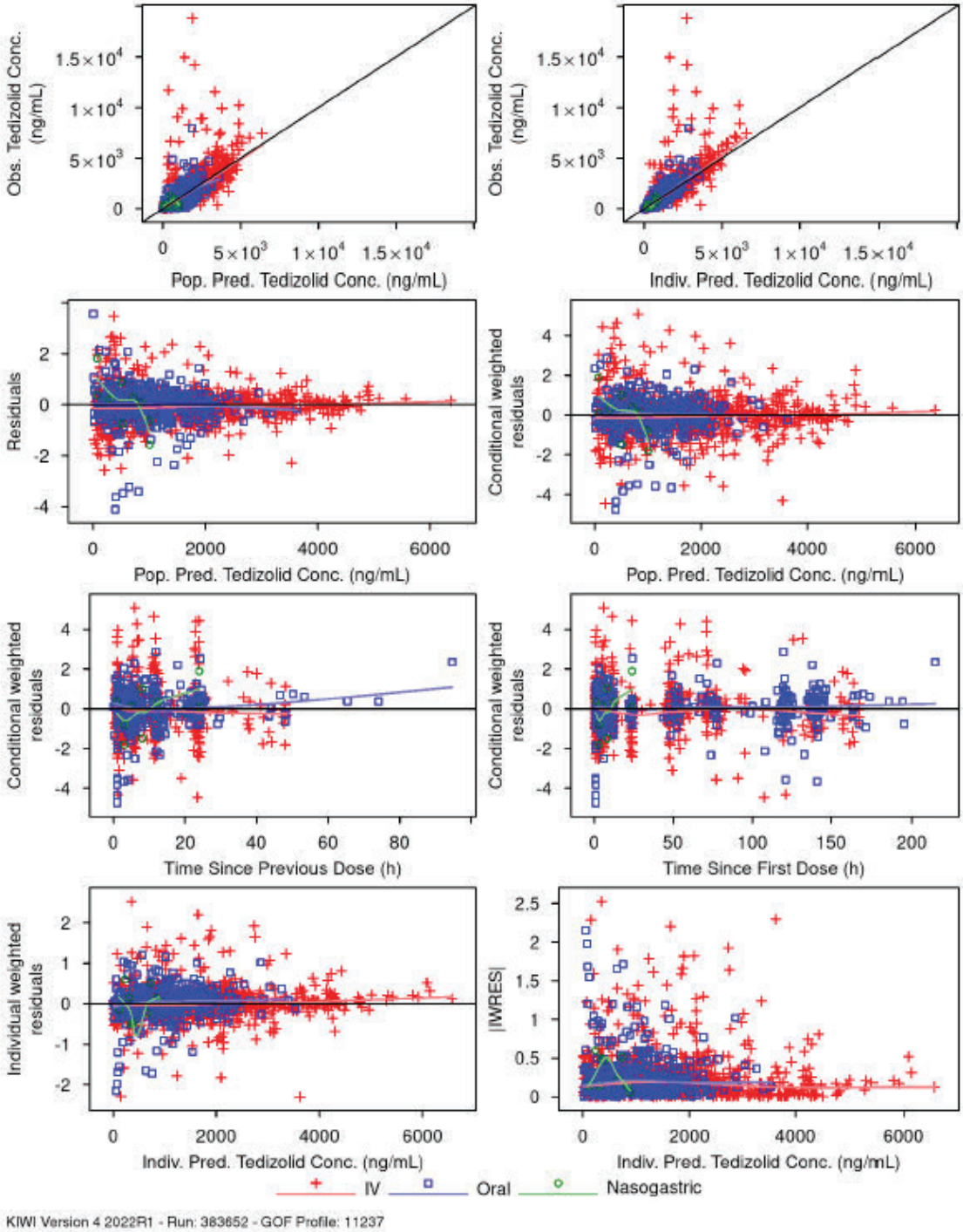
Table 47. Population Pharmacokinetic Parameter Estimates and Standard Errors for the Final Pediatric Model for Tedizolid

Parameter		Estimate	RSE (%)	IIV (%)	Shrinkage (%)
CL	Clearance (L/h)	3.71	3.02	33.9	15.7
	Body weight scale exponent[a,b]	0.770	4.85		

Parameter		Estimate	RSE (%)	IIV (%)	Shrinkage (%)
Vc	Central volume of distribution (L)	27.7	4.63	25.7	47.2
	Body weight scale exponent[a,c]	0.870	3.77		
Q	Intercompartmental clearance (L/h)	1.11	28.9		
Vp	Peripheral volume of distribution (L)	9.58	12.5		
SUSPF1	Bioavailability for oral suspension	0.854	6.34		
TABF1	Bioavailability for oral tablet	0.955	6.04		
D1	Duration for zero-order input for tablet (h)	1.90	22.7	110	65.4
ka	First-order absorption rate constant (h^{-1})	0.620	15.7	121	50.3
RV for Phase 1 IV data (variance)		0.0688	38.9		
RV for Phase 1 Oral and Phase 3 data (variance)		0.282	13.2		
Minimum Value of the Objective Function = -148.004					

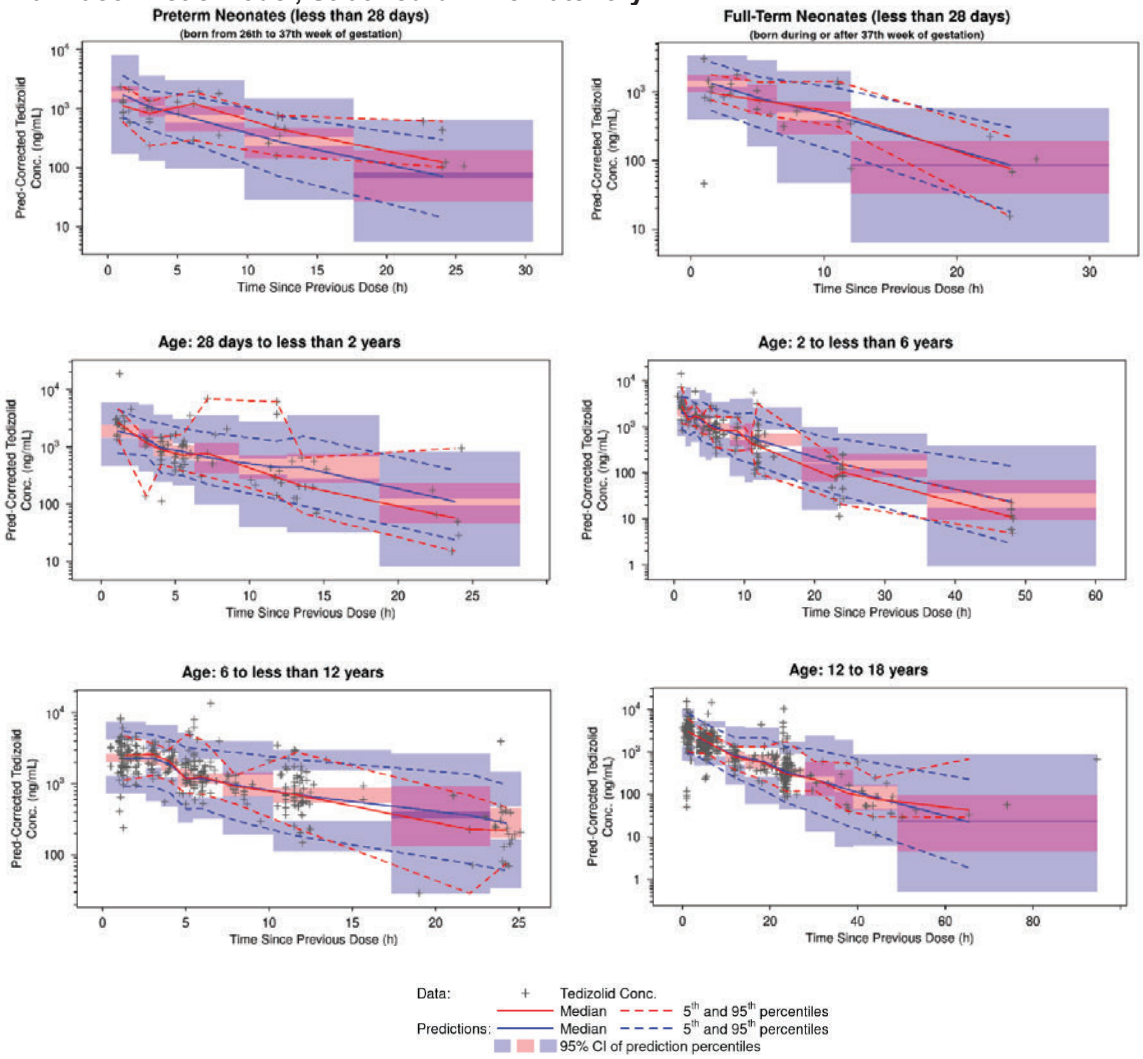
Source: Excerpt from popPK report Table 16.
[a] Normalized to 34 kg.
[b] Value of body weight scale exponent also applied to Q
[c] Value of body weight scale exponent also applied to Vp
Abbreviations: IIV, interindividual variability; IV, intravenous; %RSE, relative standard error expressed as a percent; RV, residual variability.

Figure 5. Goodness of Fit of Tedizolid Final Model Stratified by Route of Administration



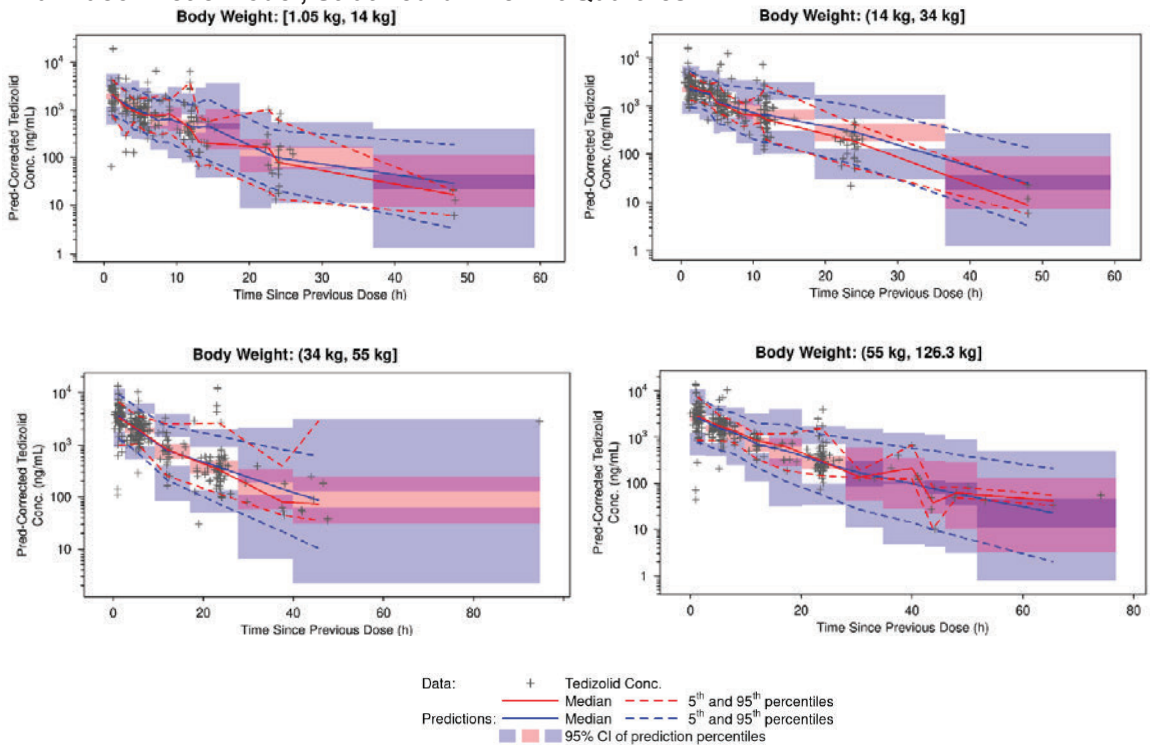
Source: Excerpt from popPK report Figure 32.

Figure 6. Prediction-Corrected Visual Predictive Check of the Final Tedizolid Population Pharmacokinetic Model, Stratified b A e Cate ory



Source: Excerpt from popPK report Figure 29.
Medians and percentiles are plotted at the median time since previous dose of the data observed within each time since previous dose.

Figure 7. Prediction-Corrected Visual Predictive Check of the Final Tedizolid Population Pharmacokinetic Model, Stratified b Wei ht Quartiles



Source: Excerpt from popPK report Figure 30
Means and percentiles are plotted at the median time since previous dose of the data observed within each time since previous dose.

Reviewer's Comments:

In general, the Applicant's popPK analysis is reasonable in capturing the central tendency of tedizolid disposition after intravenous and oral dosing. The goodness-of-fit plots showed a good agreement between the observed and the individual predicted concentrations without any obvious bias over time or predicted concentrations. The VPC plots showed that the popPK model is capturing the central tendency and the variability in tedizolid concentrations, regardless of age or route of administration. The popPK model is considered reasonable for the prediction of individual exposure metrics AUC_{0-24}, C_{max}, and C_{trough}.

17.4.3.2. Estimated Pediatric Exposure Metrics

The estimated steady-state plasma exposure metrics of tedizolid in pediatric subjects without ABSSSI (Studies MK-1986-013, MK-1986-014, and MK-1986-026) and ABSSSI patients (Studies MK-1986-018, and MK-1986-012) across all age groups are summarized in Table 48.

Table 48. Summary of Geometric Mean (%CV) of Predicted Tedizolid Steady-State Exposure Metrics, Stratified by Study

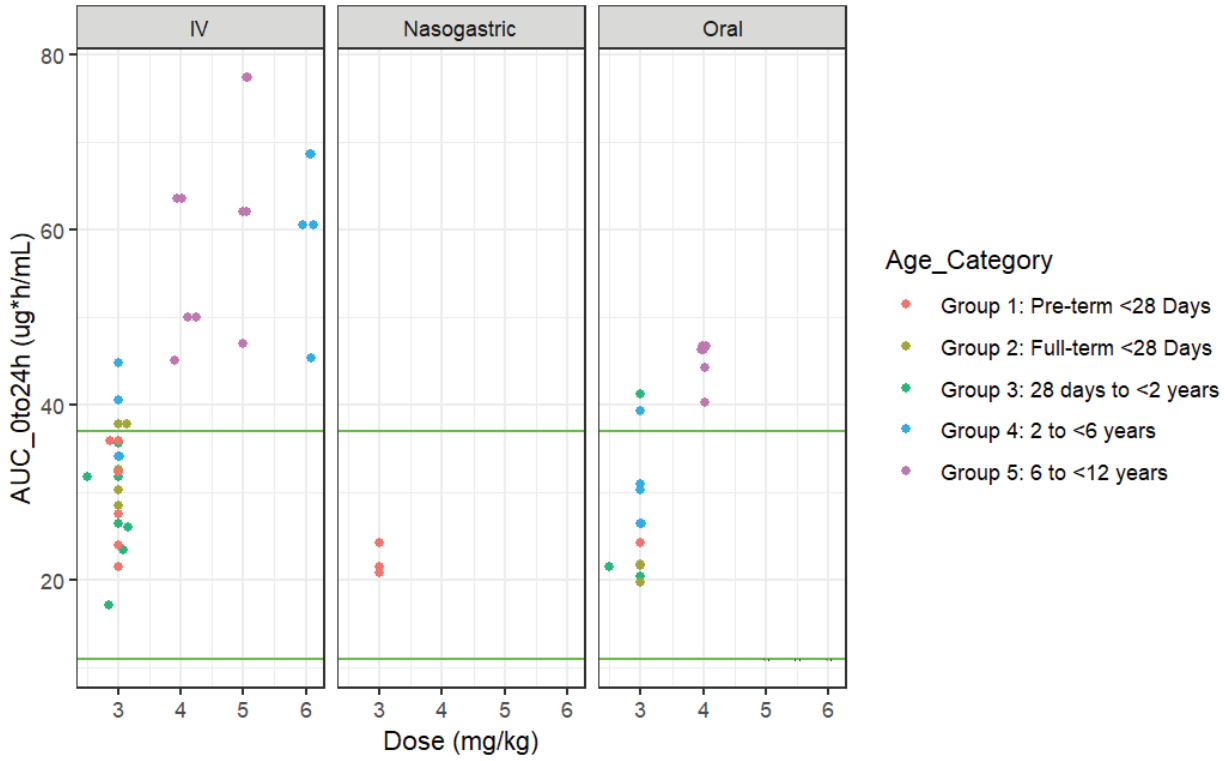
Study	MK-1986-013	MK-1986-014	MK-1986-018	MK-1986-026	MK-1986-012	
Parameter						Overall
IV dose						
N	20	23	24	10	46	123
AUC_{0-24} (h*µg/mL)	23.27 (36.97)	15.33 (35.19)	34.18 (37.26)	28.00 (22.66)	29.54 (29.89)	25.75 (43.96)
C_{max} (µg/mL)	4.38 (30.06)	2.10 (22.04)	3.00 (29.48)	3.74 (17.32)	3.70 (28.22)	3.29 (36.87)
C_{min} (µg/mL)	0.13 (79.72)	0.14 (121.02)	0.59 (71.81)	0.26 (53.71)	0.31 (68.65)	0.26 (109.26)
Oral dose						
N	12	12	49	10	43	126
AUC_{0-24} (h*µg/mL)	19.24 (28.55)	11.95 (31.43)	25.45 (32.51)	24.21 (21.50)	30.46 (27.05)	24.42 (40.62)
C_{max} (µg/mL)	1.81 (30.34)	1.09 (41.71)	1.58 (27.15)	2.05 (16.21)	2.51 (24.97)	1.85 (38.77)
C_{min} (µg/mL)	0.19 (52.26)	0.12 (85.26)	0.51 (58.93)	0.32 (66.59)	0.42 (46.20)	0.37 (78.41)

Source: Reviewer compiled from Table 26 (IV) and Table 27 (oral) from popPK report.
Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; GM, Geometric Mean; %CV, coefficient of variation expressed as a percent; N, number of subjects.

Reviewer's analysis:

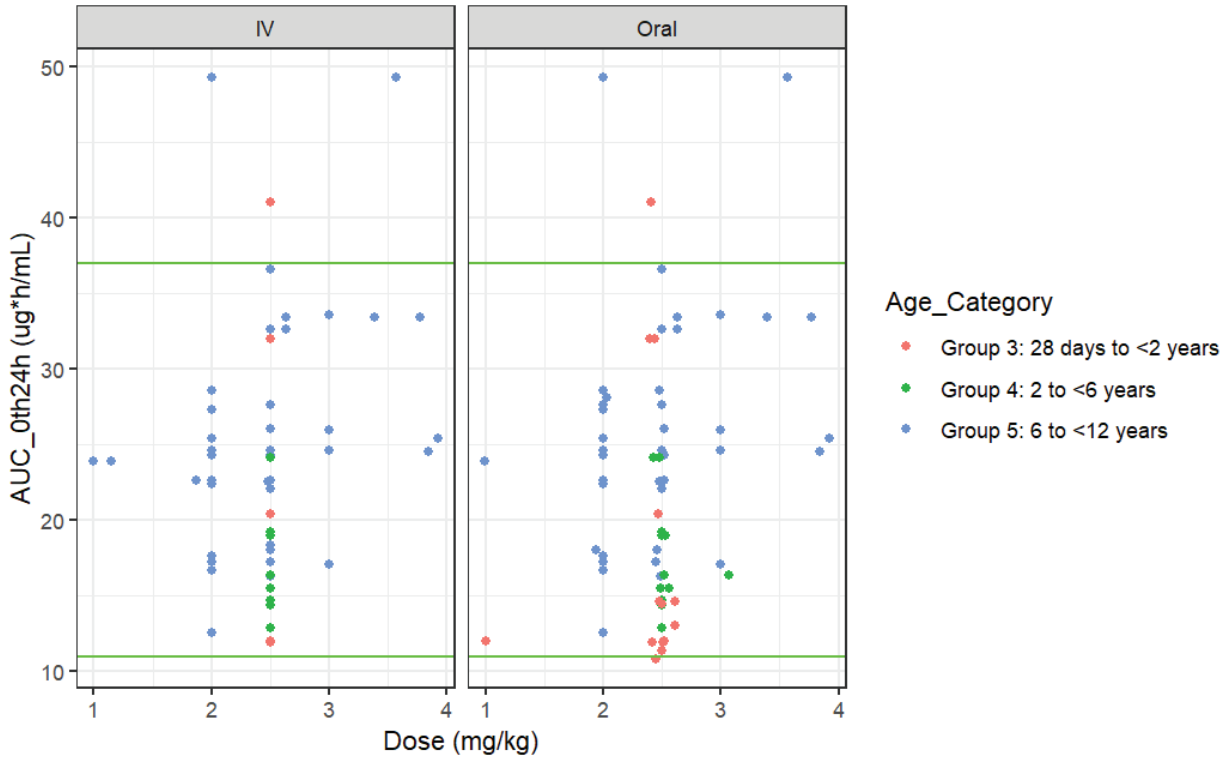
The reviewer compared the individual model-predicted tedizolid steady-state AUC_{0-24} in pediatric studies to the overall exposure (steady-state AUC_{0-24}) observed in adult ABSSSI patients, denoted by the region between the green lines in Figure 8 and Figure 9. In some age groups (2 to <12 years old) and particularly with IV administration, the steady-state AUC_{0-24} observed in pediatric trials MK-1986-013 and MK-1986-014 (Figure 8) as above the 95th percentile of steady-state AUC_{0-24} observed in adults, and this was due to the higher doses (up to 6 mg/kg) administered in these studies compared to the proposed pediatric dosing. The higher exposures from these 2 studies was supportive of safety for the proposed pediatric dosage as discussed in Section 17.4.3.2.2. In general, the exposure from Phase 3 study MK-1986-018 in pediatric patients was comparable to the exposure from the approved tedizolid phosphate dosage for adult ABSSSI patients (Figure 9).

Figure 8. Comparison of Single Dose Tedizolid Plasma AUC_{0-24} Estimated by Population PK Model in Pediatric Subjects in Study MK-1986-013 and MK-1986-014 Versus Weight-Based Dose Administered, Stratified by Route and A e Cate or , Versus Adult Phase 3 Studies



Source: Reviewer analysis.
Green lines denote adult (combined IV and oral tablet formulations) 5th and 95th percentiles of AUC_{0-24h} from Phase 3 studies.
Abbreviations: PK, pharmacokinetic

Figure 9. Comparison of Maximum Steady State Tedizolid Plasma AUC_{0-24} Estimated by Population PK Model in Pediatric Subjects in Study MK-1986-018 Versus Weight-Based Dose Administered, Stratified b Route and A e Cate or , Versus Adult Phase 3 Studies



Source: Reviewer analysis.
Green lines denote adult (combined IV and oral tablet formulations) 5th and 95th percentile of AUC_{0-24h} from Phase 3 studies.
Note: Plot reflects n=129 unique datapoints. Multiple values per participant reflects dose adjustments, IV to oral switch, or oral to IV switch, during the course of the study.
Abbreviations: PK, pharmacokinetic

17.4.3.2.1. Exploratory Pediatric Exposure Versus Clinical Response Relationship

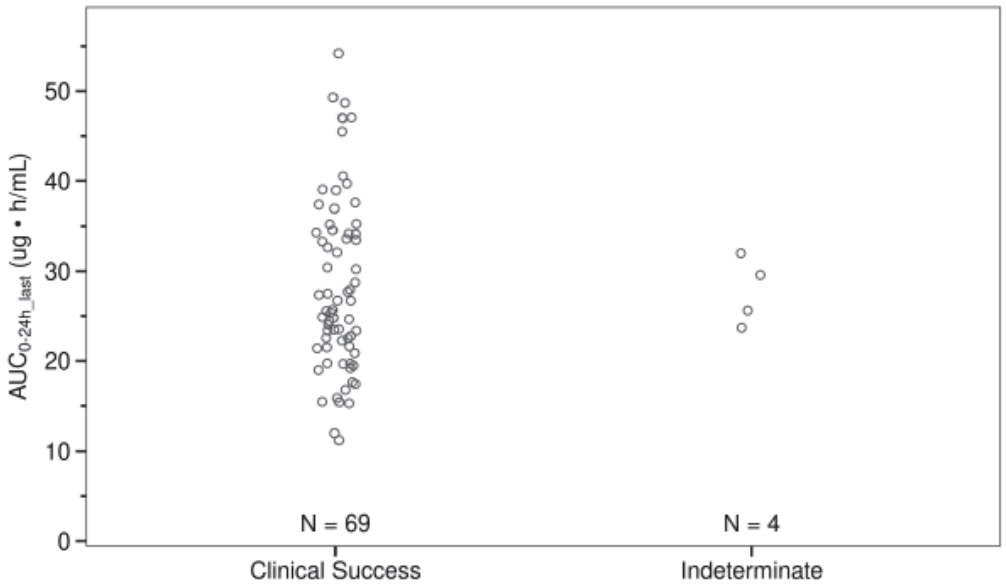
The predicted steady-state AUC_{0-24} of tedizolid in ABSSSI patients from Study MK-1986-018 was plotted against the blinded investigator assessment of the clinical response (clinical success, failure, or indeterminate, based on protocol-specified criteria) at the test of cure (TOC) visit (22 to 29 days after first dose), as shown in Figure 10. Study MK-1986-018 administered the following weight-based dosage for a minimum of 6 days, regardless of age:

- BW ≥50 kg: 200 mg dose once-daily
- BW ≥30 kg and <50 kg: 2 mg/kg doses every 12 hours
- BW 3.2 kg to <30 kg: 2.5 mg/kg doses every 12 hours

The study enrolled patients with a weight range of 6.0 to 68.0 kg, age 4 months to <12 years. The estimated steady-state AUC_{0-24} range for the actual dosage administered in Study MK-1986-018 was 12.0 to 57.1 h* µg/mL. Study MK-1986-018 blinded investigator assessment of the

clinical response at TOC was 69/73 clinical successes, 4/73 indeterminate, and no clinical failures.

Figure 10. Distribution of Tedizolid $AUC_{0\text{-}24,\ last}$ at Test of Cure in Study MK-1986-018, Stratified by Clinical Outcome



Source: Excerpt from Figure 67 from popPK report.
Abbreviations: $AUC_{0\text{-}24h}$, last area under the concentration-time curve from time 0 to 24 hours after last dose; N, number of subjects.

Reviewer's Comments:

In general, the Applicant's exploratory plot of pediatric exposure as $AUC_{0\text{-}24}$ versus clinical response observed in Study MK-1986-018 seems acceptable, suggesting the absence of an exposure-clinical efficacy relationship.

17.4.3.2.2. Pediatric Dose Recommendation

Per the current approved labeling for the commercially available SIVEXTRO (tedizolid phosphate) for injection, for intravenous use and SIVEXTRO (tedizolid phosphate) tablet, for oral use, no dose adjustments are recommended for adolescents (ages 12 to <18 years of age) or adult patients.

For the proposed expansion of the indication to pediatric patients from birth (≥26 weeks gestational age and weighing ≥1 kg) to <12 years of age, the recommended weight-band dosage is shown in Table 9. The predicted exposure metrics under the Applicant's proposed dosage are shown in Table 13.

The Applicant's proposed pediatric flat dose per weight group (Table 11 and Table 12) approximates the actual weight based (mg/kg) dosages administered in studies MK-1986-012, MK-1986-014, and MK-1986-018, as shown in Figure 11.

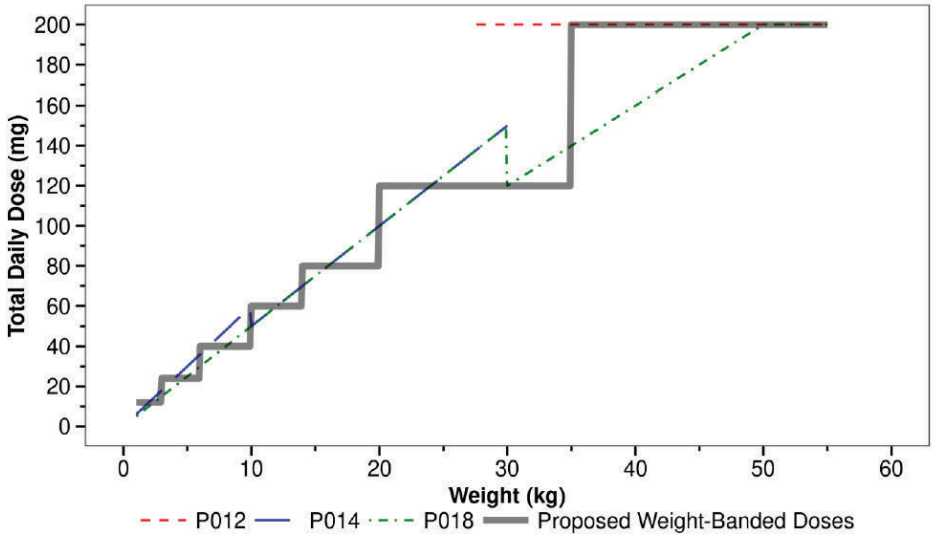
Proposed dosage for weight band ≥35 kg

Note that for pediatric patients weighing ≥35 kg the approved adult dosage is proposed. The determination of the threshold to administer the adult dose was based on actual dosages administered in Phase 3 studies MK-1986-012, and MK-1986-018 and stochastic (Monte-Carlo) simulations (per 1 kg increment of body weight) for body weights between 20 to 50 kg, administered the approved adult/adolescent dosage Figure 12 and Figure 13.

The threshold weight for administration of the approved adult/adolescent dosage (Table 11 and Table 12) is based on:

- Examination of the weight distribution of subjects ≥12 years of age in the National Health and Nutrition Examination Survey (NHANES) database, where < 1.5% of subjects ≥ 12 years of age have body weights <35 kg.
- The simulated exposures for body weights ≥35 kg were within the 5th to 95th percentile of the exposures observed in the adolescent Phase 3 study Figure 12 and Figure 13. The predicted higher C_{max} for patients weighing 35 to 42 kg after IV administration and the predicted higher AUC_{0-24} for patients weighing 35 to 42 kg after IV or oral administration, exceeding the 95th percentile of observed values in adults, were expected and in agreement with observation from studies MK-1986-026 and study MK-1986-012. As discussed in the original NDA review, a higher AUC_{0-24} and C_{max} were observed in adolescent patients 12 to <18 years of age when compared to adults when administered the approved dose of 200 mg tedizolid phosphate (IV or oral tablet formulations) in studies MK-1986-026 and MK-1986-012. The approved dosage and resulting exposures were found to be well tolerated and efficacious in adolescent patients (weight range: 28 to 126 kg).

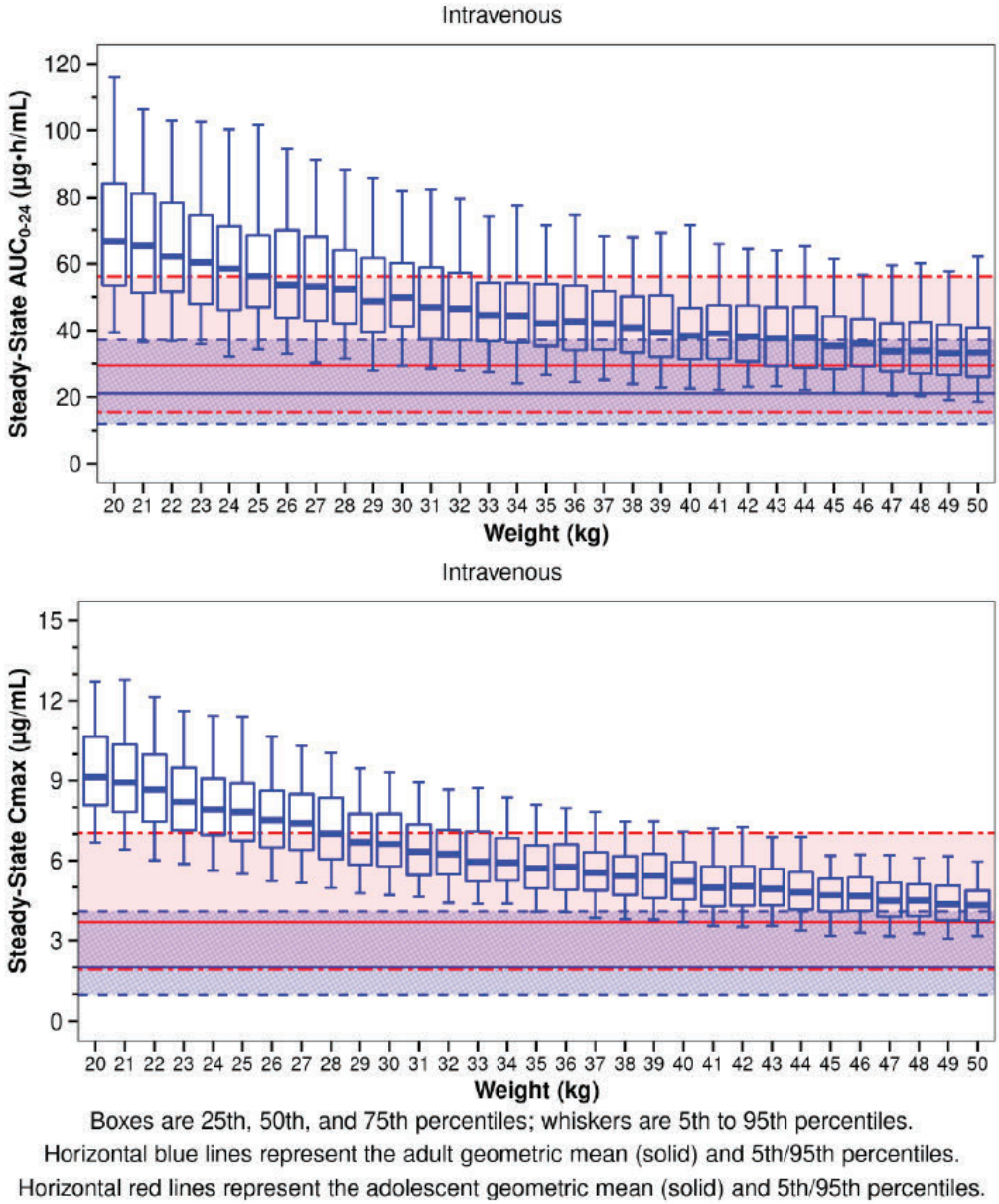
Figure 11. Comparison of the Total Daily Dose of Tedizolid Phosphate In the Proposed Weight-Banded Dosage Regimen Versus the Actual Doses Administered in Studies MK-1986-012, MK-1986-014, and MK-1986-018



In P012, dosing was fixed and not based on the body weight of the adolescent participant; the P012 line represents the range of body weights (≥ 27.6 kg) in this study.

Source: Excerpt from Figure 48 from popPK report.

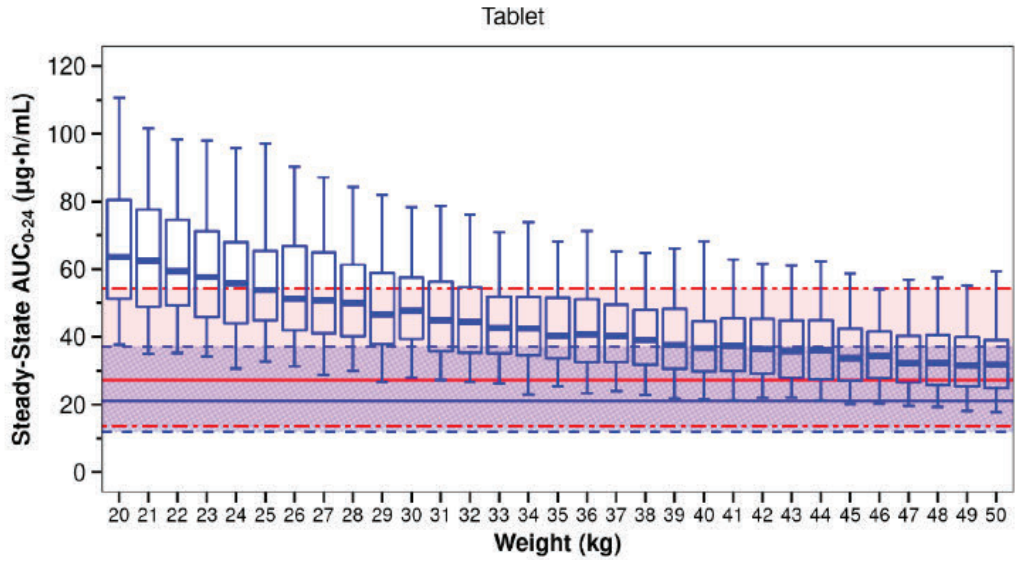
Figure 12. Comparison of Simulated Steady-State Tedizolid AUC_{0-24} and C_{max} by Body Weight Bins From 20 to 50 kg After Multiple-Dose Once-Daily Intravenous Infusions of 200 mg Tedizolid Phosphate, Versus Adult and Adolescent (Phase 3) Studies

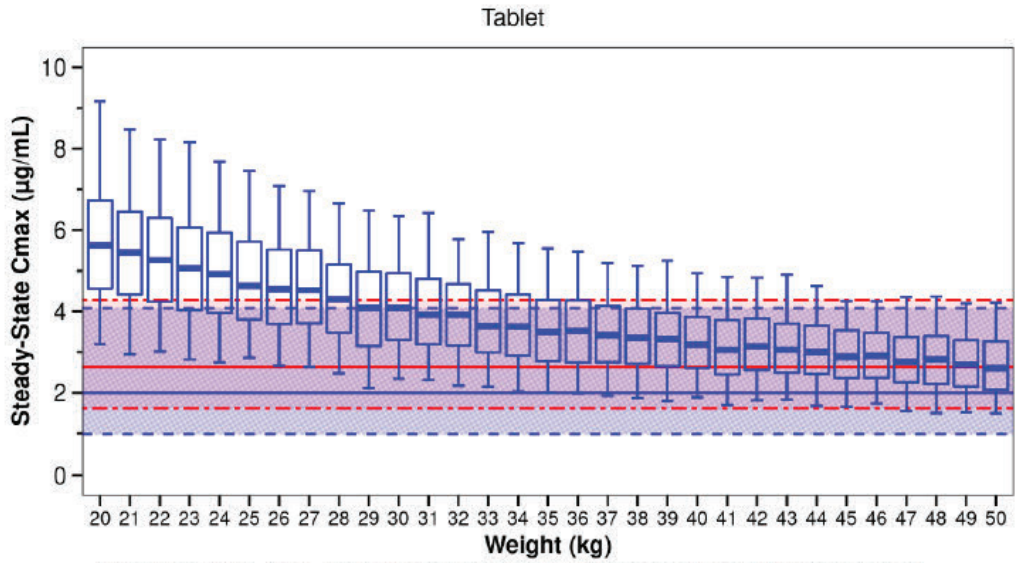


Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Horizontal blue lines represent the adult geometric mean (solid) and 5th/95th percentiles.
Horizontal red lines represent the adolescent geometric mean (solid) and 5th/95th percentiles.

Source: Excerpt from Figure 44 from popPK report
Abbreviations: AUC_{0-24}, area under the concentration- time curve from time 0 to 24 hours; C_{max}, maximum plasma concentration

Figure 13. Comparison of Simulated Steady-State Tedizolid AUC_{0-24} and C_{max} by Body Weight Bins From 20 to 50 kg After Multiple-Dose Once-Daily Oral Tablet of 200 mg Tedizolid Phosphate, Versus Adult and Adolescent (Phase 3) Studies





Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Horizontal blue lines represent the adult geometric mean (solid) and 5th/95th percentiles.
Horizontal red lines represent the adolescent geometric mean (solid) and 5th/95th percentiles.

Source: Excerpt from Figure 45 from popPK report
Abbreviations: AUC_{0-24}, area under the concentration- time curve from time 0 to 24 hours; C_{max}, maximum plasma concentration

Proposed dosage for weight bands <35 kg

The steady-state AUC_{0-24} and C_{max} at the proposed tedizolid phosphate dosage in patients with body weight <35 kg are predicted to be within the 5^{th} and 95^{th} percentile of those observed in

adults, particularly for weight bands 14 to <20 kg, 10 to <14 kg, 6 to <10 kg, and 3 to <6 kg (Figure 14).

However, for the proposed weight band of 20 to <35 kg and (b) (4) kg, the stochastic simulations (per 1 kg increment of body weight) revealed that the predicted tedizolid steady-state AUC_{0-24} exceeded the 95th percentile of those observed in adults for the following weight ranges:

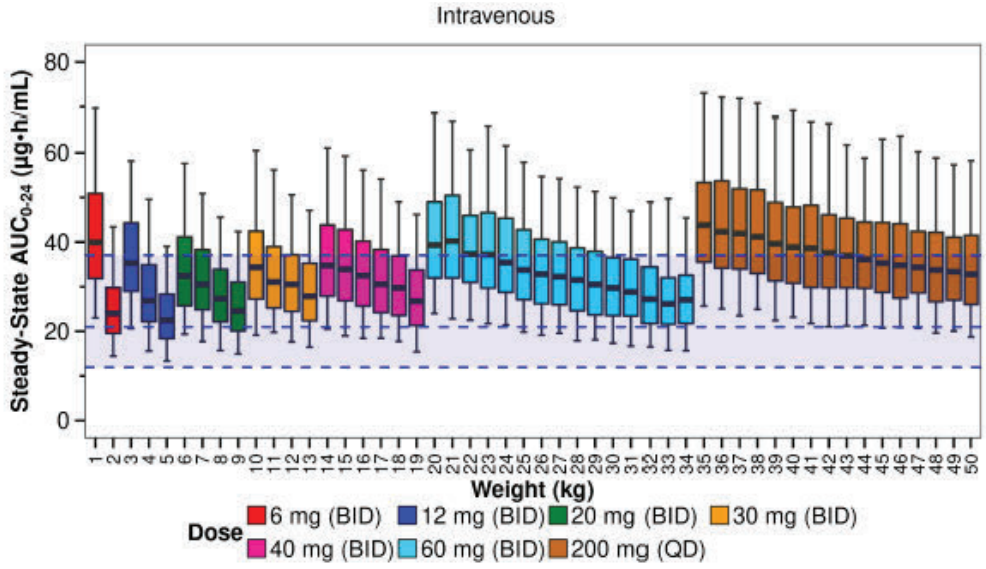
- Weights 20 to <25 kg administered 60 mg tedizolid phosphate twice daily for six days by IV infusion, corresponding to a weight-based dose range of 2.5 mg/kg to 3 mg/kg.
- Weights 1 to <2 kg administered 6 mg tedizolid phosphate twice daily for six days by IV infusion, corresponding to a weight-based dose range of 3 mg/kg to 6 mg/kg.

Although exceeding the 95th percentile of the exposure observed in adults, the following observed safety data supports the safety of administration of the proposed dosage for the 20 to 25 kg weight band:

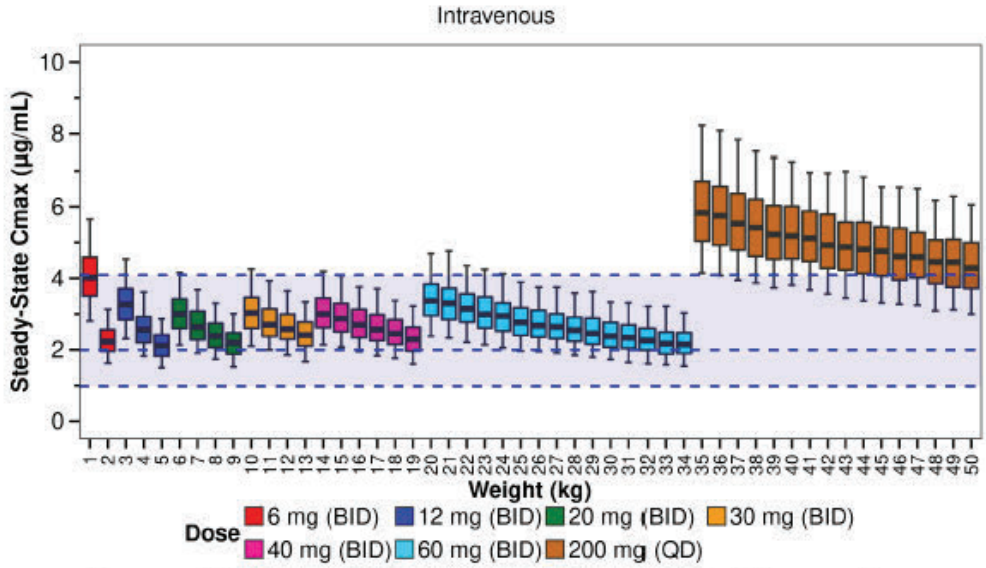
- A Phase 1 PK study MK-1986-013 found a dose of 6 mg/kg tedizolid phosphate (administered once by IV) to be well tolerated in pediatric subjects aged 2 to <6 years of age (see Section 17.4.1.1, Study MK-1986-013 Cohort 2-1). Per the NHANES August 2021 to 2023 body weight dataset, weights of 20 to 22 kg were observed in pediatric subjects aged 2 to 8 years, therefore the exposure of this Cohort is supportive of the proposed dosage for this weight band.
- A Phase 3 study MK-1986-018 found a dose of 2.5 mg/kg tedizolid phosphate twice daily for 6 days (by IV or oral suspension) to be well tolerated in pediatric patients with ABSSSI weighing 3.2 kg to <30 kg.
- The simulated exposures do not exceed the 95th percentile of the exposures observed in adolescents (studies MK-1986-026 and study MK-1986-012).

Therefore, based on the safety data from study MK-1986-013 and MK-1986-018 and the exposure in adolescents, the exposures estimated for this weight band (20 to 25 kg) supports the proposed dosage's safety from a clinical pharmacology perspective.

Figure 14. Comparison of Simulated Steady-State Tedizolid AUC_{0-24} and C_{max} Based Upon Administration of Proposed Intravenous Weight-Banded Dosage Regimen for Body Weight Bins Versus Adult Phase 3



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Horizontal blue dashed lines represent the adult geometric mean and 5th/95th percentiles.



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Horizontal blue dashed lines represent the adult geometric mean and 5th/95th percentiles.

Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; BID, twice daily; C_{max}, maximum plasma concentration; QD, once daily.

Source: Excerpt Figure 49 popPK report.

In contrast, there is lack of adequate observed safety data for the proposed dosage of (b) (4) tedizolid phosphate twice daily by IV in pediatric patients weighing 1 to <2 kg (weight-based dosing range of (b) (4) mg/kg). The following clinical studies included neonate subjects:

- A Phase 1 PK study MK-1986-014 found that a dose of 2.5 to 3 mg/kg tedizolid phosphate (administered once by IV) to be well tolerated in subjects with ages ranging from (b) (4) (preterm and term neonates) to <2 years old (weights: 1.05 to 14 kg).
- A Phase 3 study MK-1986-018 found that a dose of 2.5 mg/kg tedizolid phosphate twice daily for 6 days (IV or oral suspension) was well tolerated in pediatric patients with ABSSSI (weighing 3.2 kg to <30 kg). No patients aged <28 days were enrolled in the study and the lowest weight patient enrolled was 6 kg.

We note that patients weighing between 1 to <2 kg represent a very vulnerable subgroup who are likely premature on the first day of life. In addition, typical weight variations in neonates during the course of the treatment further increases uncertainties. Therefore, the FDA review team recommended that the Applicant's proposed dosage for this weight band be revised.

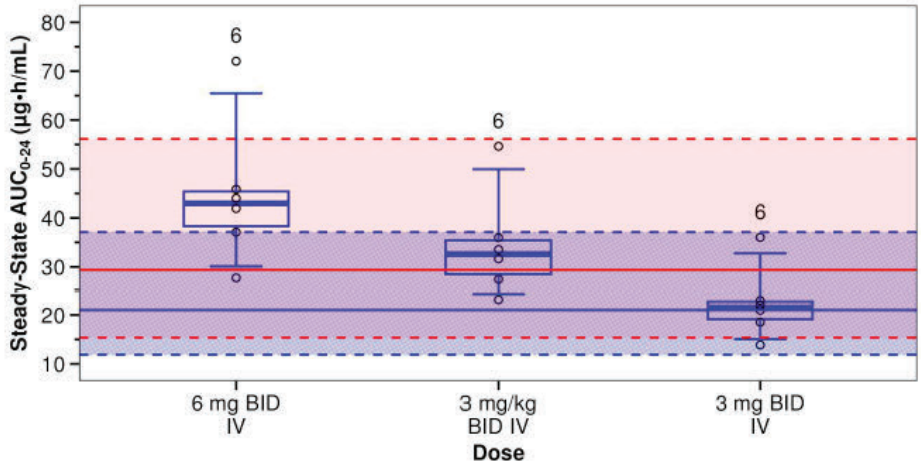
The FDA proposed a revision of the dosage to either 3 mg or 3 mg/kg tedizolid phosphate by IV twice daily for 6 days for the weight band of 1 to <2 kg and 6 mg for the weight band of 2 to <3 kg. Figure 15 shows that the revised dosages for the weight band 1 to <2 kg are expected to result in steady-state AUC_{0-24} within the 5th to 95th percentile of adult exposures. The Applicant's and FDA's agreed upon revised dosage is shown in Table 49.

Table 49. Applicant' Revised Proposed Weight-Band Intravenous Dosage of SIVEXTRO for Pediatric Patients with ABSSSI

Weight band (kg)	Dose	Frequency	Infusion time	Duration
1 to <2	3 mg/kg	Twice daily	1 hour	6 days
2 to <3	6 mg	Twice daily	1 hour	6 days

Source: Reviewer compiled.
Abbreviations: ABSSSI, Acute Bacterial Skin and Skin Structure Infections

Figure 15. Comparison of Simulated Steady-State Tedizolid AUC_{0-24} Boxplots Based Upon Administration of 3 potential dosage regimens in Neonate Subjects from MK-1986-014 With Body Weights 1 to <2 kg Versus Adult and Adolescent Phase 3) Studies



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
The number of subjects is above each box.
Horizontal blue lines represent the adult geometric mean (solid) and 5th/95th percentiles.
Horizontal red lines represent the adolescent geometric mean (solid) and 5th/95th percentiles.

Source: Excerpt Figure 1 Clinical Information Amendment submitted January 27, 2025.

Reviewer's comments:

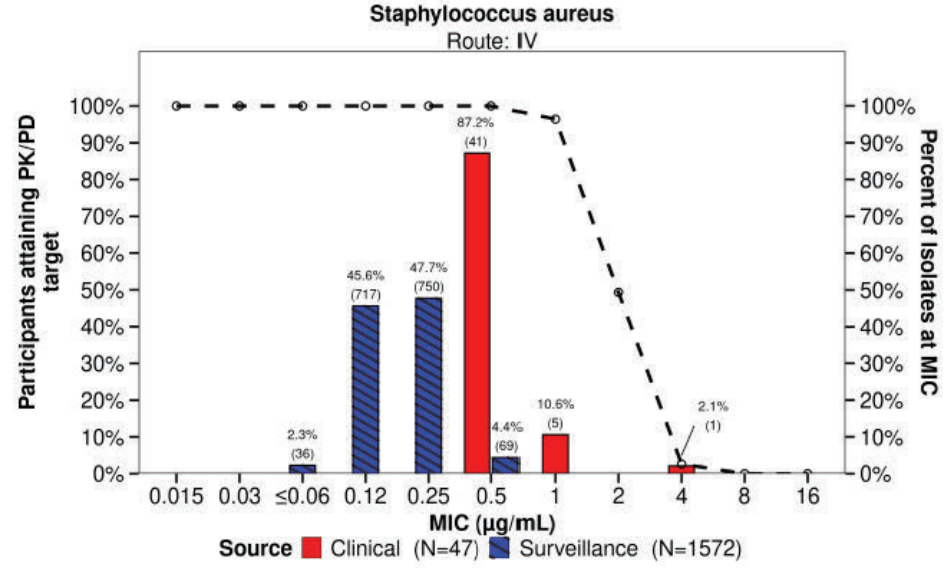
Based on the Reviewer's independent evaluation of pediatric exposure based on the popPK model, the Reviewer agrees with the recommended pediatric weight-band dosage shown in Table 9. The Applicant's initial proposed dosage did not have sufficient safety data to support the proposed dosage in patients weighing 1 to <2 kg. The FDA and Applicant negotiated a revised dosage which did have clinical data of the dosage in the neonate population to support safety and resulted in exposures comparable to those observed in adults in Phase 3 studies, as discussed in Section 6.2.1.

17.4.3.2.3. Probability of Target Attainment Estimated for Proposed Weight-Band Dosage

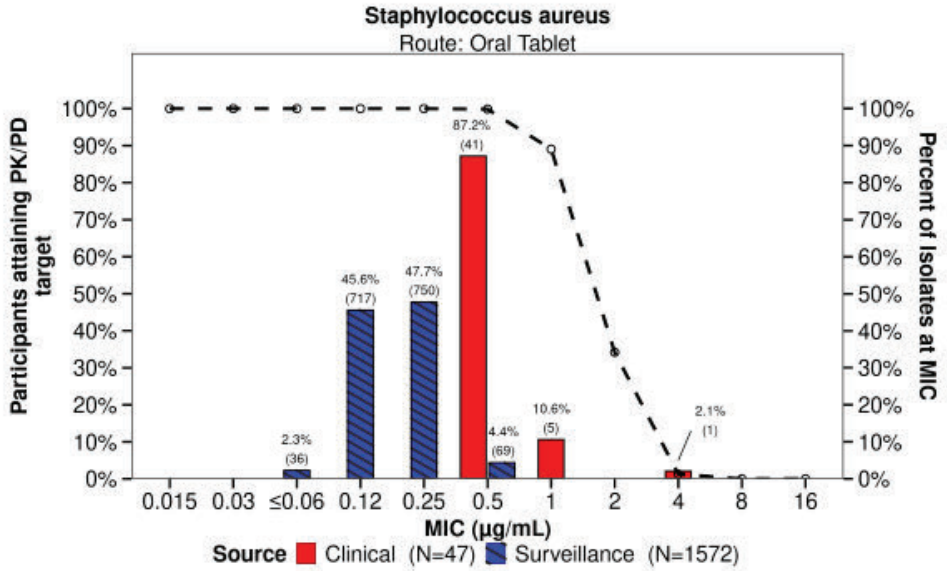
The Applicant's PK/PD target (determined from animal infection models) was tedizolid free drug AUC (*f*AUC) divided by the MIC of the infecting organism to be equal or greater than 3 (*f*AUC/MIC > 3), across the defined range of MIC values from 0.015 to 16 µg/mL. Monte Carlo simulations were used to predict tedizolid *f*AUC and calculate the probability of PTA for each MIC, for the proposed weight band dosage in a virtual pediatric population of 4000 subjects (1000 per age group) sampled from the NHANES database.

The Applicant's simulation predicted tedizolid to have 100 % PTA in pediatric patients up to the susceptibility breakpoint MIC of 0.5 µg/mL (see Figure 16 and Figure 17).

Figure 16. Probability of Target Attainment Curve for the Virtual Pediatric Population for the Proposed Weight-Banded Dosage, Overlaid on the Distribution of Minimum Inhibitory Concentration Values



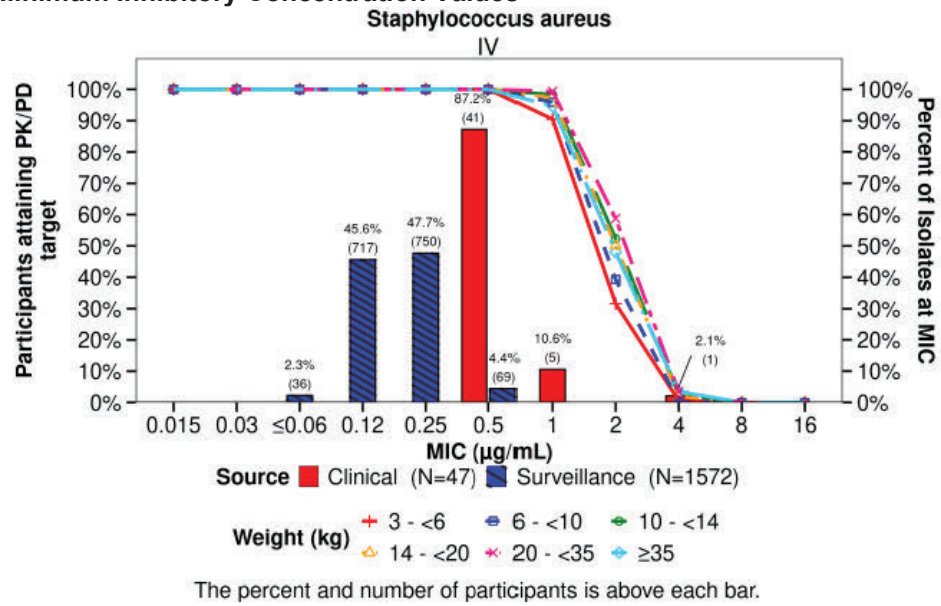
Abbreviations: IV, intravenous; MIC, minimum inhibitory concentration; N, number of participants; PK/PD, pharmacokinetic/pharmacodynamic.



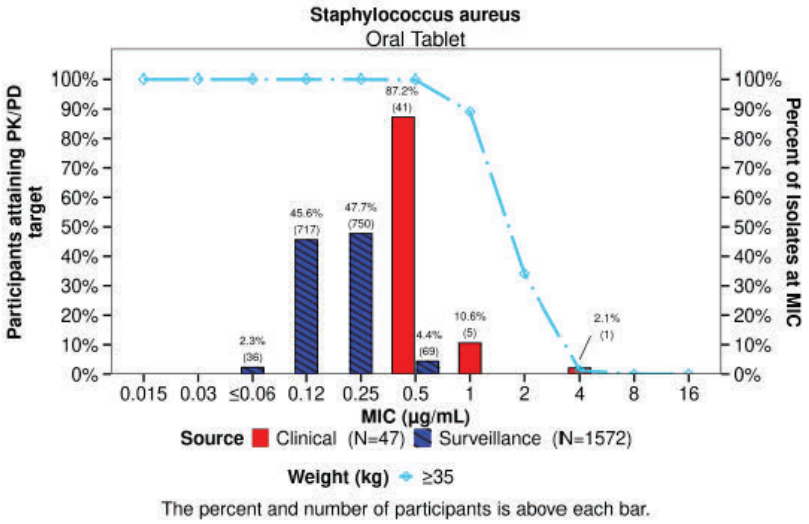
Abbreviations: MIC, minimum inhibitory concentration; N, number of participants; PK/PD, pharmacokinetic/pharmacodynamic.

Source: Excerpt Figure 63 and 64 popPK report.

Figure 17. Probability of Target Attainment Curve for the Virtual Pediatric Population for the Proposed Weight-Banded Dosage, Stratified by the Weight-Bands, Overlaid on the Distribution of Minimum Inhibitory Concentration Values



Abbreviations: IV, intravenous; MIC, minimum inhibitory concentration; N, number of participants; PK/PD, pharmacokinetic/pharmacodynamic.



Source: Excerpt Figure 65 and 66 popPK report.
Abbreviations: MIC, minimum inhibitory concentration; N, number of participants; PK/PD, pharmacokinetic/pharmacodynamic

Reviewer's comments:

Although, the Applicant's PTA analysis was supportive of the efficacy for tedizolid, the approval in the pediatric population <12 years of age is based on exposure comparison to adults and adolescents. Based on the Reviewer's independent evaluation of pediatric exposure, PTA and

safety based on the popPK model, the Reviewer agrees with the recommended pediatric weight-band dosage shown in Table 9, as discussed in Section 17.4.3.2.2.

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/s/

MARK S NEEDLES
04/03/2025 02:38:11 PM

PETER W KIM
04/04/2025 09:42:29 AM