NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental new drug applications
Application Numbers	NDA 205435/S012 and NDA 205436/S007
Priority or Standard	Standard
Submit Dates	August 19, 2019
Received Dates	August 19, 2019
PDUFA Goal Date	June 19, 2020
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	June 16, 2020
Established/Proper Name	Tedizolid
Trade Name	Sivextro
Pharmacologic Class	Oxazolidinone
Applicant	Cubist Pharmaceuticals LLC, a subsidiary of Merck & Co., Inc.
Dosage form	Tablet and Injection
Applicant proposed Dosing Regimen	200 mg administered once daily orally or as an intravenous (IV) infusion over 1 hour for six (6) days
Applicant Proposed Indication/Population	Pediatric patients 12 years of age to less than 18 years of age, for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria.
Regulatory Action	Approval

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Deborah Wang
Chief, Regulatory Project Management Staff	Carmen DeBellas
OPQ Reviewer	Ramesh Gopalaswamy
OPQ Team Leader	Gurpreet Gill-Sangha
Office of Clinical Pharmacology Reviewer(s)	Cristina Miglis, Jihye Ahn
Office of Clinical Pharmacology Team Leader(s)	Zhixia Danielsen, Justin Earp
Clinical Reviewer	Mayurika Ghosh, Amy Bishara
Clinical Team Leader	Thomas Smith
Clinical Microbiology Reviewer	Simone Shurland
Clinical Microbiology Team Leader	Avery Goodwin
Statistical Reviewer	Christopher Kadoorie
Statistical Team Leader	Karen Higgins
Cross-Disciplinary Team Leader	Thomas Smith
Division Director	Sumathi Nambiar

Additional Reviewers of Application

OPDP	David Foss
OSI	Xiaohan Cai

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
OPQ Reviewer	Ramesh Gopalaswamy	OPQ/OLDP	Sections: 4.2	**Select one:** __x__ Authored ___ Approved
	Signature:	***{See appended electronic signature page}***		
OPQ Team Leader	Gurpreet Gill-Sangha	OPQ/OLDP	Sections: 4.2	**Select one:** ___ Authored __x__ Approved
	Signature:	***{See appended electronic signature page}***		
Clinical Pharmacology Reviewer	Cristina Miglis	OCP/DCPIV	Section: 4.3.3, 6	**Select one:** __x__ Authored ___ Approved
	Signature: ***{See appended electronic signature page}***			
Clinical Pharmacology Team Leader	Zhixia Danielsen	OCP/DCPIV	Section: 4.3.3, 6	**Select one:** ___ Authored __x__ Approved
	Signature: ***{See appended electronic signature page}***			
Pharmacometrics Reviewer	Jihye Ahn	OCP/DPM	Section: 6, 16.2	**Select one:** __x__ Authored ___ Approved
	Signature: ***{See appended electronic signature page}***			
Pharmacometrics Team Leader	Justin Earp	OCP/DPM	Section: 6, 16.2	**Select one:** ___ Authored __x__ Approved
	Signature: ***{See appended electronic signature page}***			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Mayurika Ghosh	OID/DAI	Sections: 1, 2, 3, 4.1, 5, 7, 8.2, 9, 10, 11, 16 Sections: 4.3.1,4.3.2,4.3.4,5,8.1	**Select one:** __x__ Authored __x__ Approved
	Signature: ***{See appended electronic signature page}***			
Clinical Reviewer	Amy Bishara	OID/DAI	Sections: 4.3.1,4.3.2,4.3.4,5,8.1	**Select one:** __x__ Authored ___ Approved
	Signature: ***{See appended electronic signature page}***			
Clinical Team Leader	Thomas Smith	OID/DAI	Sections: 1, 2, 3, 4.1, 4.3.1,4.3.2,4.3.4,5, 5, 7, 8.1, 8.2,9, 10, 11, 16	**Select one:** ___ Authored __x__ Approved
	Signature: ***{See appended electronic signature page}***			
Statistical Reviewer	Christopher Kadoorie	OB/DBIV	Sections: 7, 8	**Select one:** __x__ Authored ___ Approved
	Signature: ***{See appended electronic signature page}***			
Statistical Team Leader	Karen Higgins	OB/DBIV	Sections: 7, 8	**Select one:** ___ Authored __x__ Approved
	Signature: ***{See appended electronic signature page***			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Microbiology	Simone Shurland	OID/DAI	Sections: 4.3.1, 4.3.4	**Select one:** __x__ Authored ___ Approved
	Signature: ***{See appended electronic signature page}***			
Clinical Microbiology Team Leader	Avery Goodwin	OID/DAI	Sections: 4.3.1, 4.3.4	**Select one:** ___ Authored __x__ Approved
	Signature: ***{See appended electronic signature page}***			
Associate Director for Labeling	Abimbola Adebowale	OID/DAI	Section 11	**Select one:** ___ Authored __x__ Approved
	Signature: ***{See appended electronic signature page}***			
Regulatory Project Manager	Deborah Wang	ORO/DRO-ID	Sections: 3	**Select one:** ___ Authored __x__ Approved
	Signature: ***{See appended electronic signature page}***			
Chief, Regulatory Project Management Staff	Carmen DeBellas	ORO/DRO-ID	Sections: 3	**Select one:** ___ Authored __x__ Approved
	Signature: ***{See appended electronic signature page}***			
Division Director (Clinical)	Sumathi Nambiar	OID/DAI	Section: 1	**Select one:** ___ Authored __x__ Approved
	Signature: ***{See appended electronic signature page}***			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Tedizolid phosphate (Sivextro) is a member of the oxazolidinone class of antibacterials drugs. Tedizolid phosphate is a prodrug that is rapidly converted in vivo by phosphatases to the active entity, tedizolid. Tedizolid acts by binding to the 50S subunit of the bacterial ribosome, resulting in inhibition of protein synthesis. Tedizolid has demonstrated activity in vitro and in vivo against Gram-positive organisms, including staphylococci (e.g., both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*) and streptococci (e.g., *Streptococcus pyogenes*). Tedizolid is approved in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) as tedizolid 200 mg tablets orally once daily for 6 days and tedizolid 200 mg intravenously (IV) once daily for 6 days.

These supplemental new drug applications (sNDAs) propose to expand the use of tedizolid phosphate in the treatment of ABSSSIs to a new population: pediatric patients aged 12 to less than 18 years of age. The Applicant proposes to use the same dose for tablets and injection as approved in adults.

1.2. Conclusions on the Substantial Evidence of Effectiveness

These sNDAs present data from Study MK-1986-012, a randomized, single-blind, multicenter study comparing the safety and efficacy of tedizolid phosphate 200 mg IV or orally per day for six days to comparators administered IV or orally for 10 days for the treatment of ABSSSI in patients aged 12 years to less than 18 years of age. The primary objective was to evaluate the safety and tolerability of tedizolid. The trial was not powered for comparative inferential efficacy analysis. Use of tedizolid for the treatment of ABSSSI in adolescents is supported by extrapolation of evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data.

The primary efficacy endpoint was clinical response (per blinded investigator's assessment) at the TOC visit (18-25 days after first dose of study drug) in the ITT and CE populations. The primary efficacy results were favorable, with clinical success rates of 96.7% in the tedizolid arm versus 93.1% in the comparator arm, with a treatment difference (tedizolid minus comparator) of 3.6% at the test of cure visit (TOC) in the intent to treat (ITT) population. In the clinically evaluable (CE) population, success rates were 100% versus 96.3%, with a difference of 3.7%. Findings in other efficacy endpoints were supportive of primary analysis findings. Adverse reactions in adolescent patients included phlebitis (3%), increased hepatic transaminases (3%), and vomiting (1%). There were no deaths, and no serious adverse events were related to tedizolid administration. The safety profile of tedizolid in adolescents is comparable to that in adults.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Tedizolid was approved for adults with ABSSSI in 2014 and is available in both IV and oral formulations. These sNDAs expand the indication for use in adolescents 12 years of age and older at the approved adult dose of 200 mg administered once daily orally or as an IV infusion over 1 hour for six days. The Applicant has conducted a randomized (3:1), multicenter, evaluator-blinded, safety and efficacy study of tedizolid phosphate for 6 days versus comparator therapy (administered IV and/or orally for 10 days) for the treatment of suspected or documented gram-positive ABSSSI in 120 patients, 12 years to less than 18 years of age.

The primary efficacy endpoint was clinical response (per blinded investigator's assessment) at the TOC visit (18-25 days after first dose of study drug) in the ITT and CE populations. Clinical success rates in the ITT population at the TOC visit were 88/91 (96.7%) in the tedizolid arm versus 27/29 (93.1%) in the comparator arm, with a treatment difference (tedizolid minus comparator) of 3.6%. In the CE-TOC population, success rates were 87/87 (100%) versus 26/27 (96.3%), with a difference of 3.7% (95% CI: -3.4%, 10.8%). These findings were robust to the choice of the analysis sets and time points. Findings in other efficacy endpoints were supportive of primary analysis findings.

Adverse reactions in adolescent patients included phlebitis (3%), increased hepatic transaminases (3%), and vomiting (1%). There were no deaths, and no serious adverse events were related to tedizolid administration. The safety profile of tedizolid in adolescents is comparable to that in adults. 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 patients aged 12 years and older. Availability of tedizolid for use in adolescents will add to the armamentarium of products available for the treatment of ABSSSI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ABSSSIs include cellulitis/erysipelas, wound infections, and major cutaneous abscesses, which are most commonly caused by *S. aureus* and beta-hemolytic streptococci in pediatric and adult patients worldwide. ABSSSIs caused by resistant organisms, particularly MRSA, are of increasing concern due to the limited treatment choices. ABSSSIs are seen in all pediatric age groups. The profile of causative ABSSSI pathogens is the same for adolescent and adult infections. The severity of illness ranges from mild to severe infections.	ABSSSIs are common, serious bacterial infections that can cause significant morbidity.
Current Treatment Options	• There are many therapies available for treatment of ABSSSIs 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 development of antibacterial resistance. • Oral antibacterial options for treating skin and soft-tissue infections in patients with community-associated MRSA include clindamycin, trimethoprim/sulfamethoxazole, a tetracycline, 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 adolescents will add to the armamentarium of products available for ABSSSI.
Benefit	• Study MK-1986-012 is a 3:1 randomized, multicenter, safety and efficacy study of tedizolid phosphate (200 mg administered IV and/or orally once a day for 6 days) versus comparator therapy (administered IV and/or orally for 10 days) for the treatment of suspected or documented gram-positive ABSSSI in 120	• 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 patients aged 12 years and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	participants 12 years to less than 18 years of age. The comparators included vancomycin, cefazolin, linezolid, clindamycin, and others. • The primary efficacy endpoint was clinical response (per blinded investigator's assessment) at the TOC visit (18-25 days after first dose of study drug) in the intent to treat (ITT) and clinically evaluable (CE) populations. • The secondary efficacy endpoints were early clinical response at 48- 72 hours (20% or more lesion size reduction) and clinical response (per blinded investigator's assessment) at the EOT (end of treatment) visit. • Clinical success rates in the ITT population at the TOC visit were 88/91 (96.7%) in the tedizolid arm versus 27/29 (93.1%) in the comparator arm, with a treatment difference (tedizolid minus comparator) of 3.6% (95% CI: -6.3%, 13.5%). In the CE-TOC population, success rates were 87/87 (100%) versus 26/27 (96.3%), with a difference of 3.7% (95% CI: -3.4%, 10.8%). • Responder rates at the 48-72 hour visit were 92.3% in the tedizolid arm versus 96.6% in the comparator arm, a difference of -4.2% (-12.9%, 4.4%). Clinical success rates at EOT were 97% in both arms.	older. • This study showed a high rate of clinical success at the TOC visit which was similar in the tedizolid and comparator arms. Findings in other efficacy endpoints were supportive of primary analysis findings. Microbiological success rates were high overall and similar between treatment arms. Results from this trial support the efficacy of tedizolid in the treatment of ABSSSI in adolescents.
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 *Clostridioides difficile*-associated diarrhea.	• The safety profile of tedizolid in adolescents is comparable to that in adults. • Risks have been adequately conveyed in labeling. No additional risk mitigation strategies are needed at this time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The safety population in this trial included 120 patients, 91 treated with tedizolid and 29 treated with comparators. with no deaths or serious adverse events deemed related to tedizolid. • Treatment emergent adverse events (TEAEs) in the tedizolid arm (14.3%) were numerically slightly higher than in the comparator arm (10.3%). • Adverse reactions in adolescent patients receiving tedizolid included phlebitis (3%), increased hepatic transaminases (3%), and vomiting (1%). The phlebitis was noted with the injection formulation. • There were no deaths, and no serious adverse events were related to tedizolid administration.	

1.4. Patient Experience Data

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

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Subject Reported Outcome assessment (pain), see section 8 Palatability scale
		□	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):		
□	**Patient experience data was not submitted as part of this application.**			

Patients were asked if they liked or disliked the medication on a 5 point hedonic scale. Pain was assessed throughout the study on the Baker-Wong scale.

2 Therapeutic Context

2.1. Analysis of Condition

ABSSSIs 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%[1]. Among inpatients, *S. aureus* accounts for approximately 70% of cutaneous abscess and ABSSSI with additional complicating factors, with MRSA accounting for approximately 45% [2]. ABSSSIs range in severity from mild localized infections to severe infections with signs and symptoms of systemic toxicity. Currently, ABSSSIs are 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 is estimated at 10-11% and at 5-8% due to carbuncles and furuncles[3]. Among pediatric groups, ABSSSIs are seen from premature infants to teenagers, without predilection for a particular age subset. The profile of causative ABSSSI pathogens is the same across 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, a tetracycline, and linezolid.

[1] Talan DA et al. Comparison of *Staphylococcus aureus* from skin and soft tissue infections in US emergency department patients, 2004 and 2008. Clin Infect Dis 2011;53:144-149.
[2] Jenkins TC et al. Skin and soft tissue infections requiring hospitalization at an academic medical center: opportunities for antimicrobial stewardship. Clin Infect Dis 2010;51:895-901.
[3] Spellberg B et al. Antimicrobial agents for complicated skin and skin structure infections: justifications of non-inferiority margins in the absence of placebo-controlled trials. Clin Infect Dis 2009;49:383-391.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

3.2. Summary of Presubmission/Submission Regulatory Activity

June 20, 2014: SIVEXTRO® (tedizolid phosphate) tablet and injection were approved for treatment of ABSSSI in adult patients. Several Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) were issued, including 2159-1, which was to "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 of Acute Bacterial Skin and Skin Structure Infections in Pediatric Patients Aged 12 to <18 Years." This study (MK-1986-012) is submitted to fulfill PREA PMR 2159-1. For details about other PMRs, refer to section 10 (Pediatrics).

October 27, 2014: The pediatric study plan was filed prior to the NDA approval and the final protocol for the MK-1986-012 study was submitted.

January 29, 2018: Deferral extension requests due to enrollment issues were granted.

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

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) and the Office of Regulatory Affairs (ORA) inspected the analytical portion of study MK-1986-012 (NDA 205435/S012 and NDA 205436/S07, Tedizolid Phosphate Tablet and Injection) conducted at [redacted] and concluded that no action was indicated. A Form 483 was not issued. Although certain issues were noted during inspection, e.g., standard operating procedure deviation and lack of expiration date on a reference lot, [redacted] committed to corrective actions which were found acceptable to OSIS. Unexpired reference lots were used to test the samples, as noted in OSIS and ORA review, dated April 3, 2020. The overall conclusion from the inspection of the bioanalytical sites was that it did not affect the data reliability or integrity of the phase 3 study.

4.2. Product Quality

Tedizolid phosphate is formulated as a sterile lyophilized powder for reconstitution, dilution and injection (200 mg/vial). The 200 mg tablets of tedizolid phosphate are immediate-release film-coated tablets. In the recent annual report, prior to submission of this supplement, there were no changes in excipients or reports of concerns by the Applicant during the manufacturing process that would affect the purity or quality of the drug product or substance. The Applicant had provided updated stability data for drug product and substance.

For the expanded indication proposed in this supplement, the Applicant proposes to use the currently approved and marketed drug products, Sivextro (tedizolid phosphate) for injection, and Sivextro (tedizolid phosphate) tablet. Hence, there is no new product quality (CMC) information provided with this supplement submission.

The Applicant's request for a categorical exclusion from the requirement of an environmental assessment for this supplement is acceptable, based on the applicant's statement that no extraordinary circumstances exist to its knowledge and the estimated value of EIC-Aquatic = [redacted] ppb (*well below the 1 ppb threshold*; ref: FDA Environmental Assessment guidance).

Product quality related labeling revisions recommended are as follows:

- Change term [redacted] to "single-dose vial" for Sivextro IV, per the "Package Type Terms" guidance
- Inclusion of a "discard" statement (Section 2.2 of FPI, and Sivextro IV vial & carton)
- Inactive ingredients in the drug products (tablet and IV) to be listed in alphabetical order per the requirements of USP <1091> [FPI (Section 11) and PPI]
- Addition of a statement on concentration and pH (range) of the reconstituted solution of Sivextro IV (Section 11 of FPI)

It is expected that all the labeling recommendations will be implemented before the approval of this supplement.

Based on the discussions above, the changes proposed in this supplement are not expected to adversely impact on the quality of the Sivextro drug products, and on patient safety. This supplement submission is recommended for approval from a Product Quality perspective.

Refer to the CMC review in Panorama for full details.

4.3. Clinical Microbiology

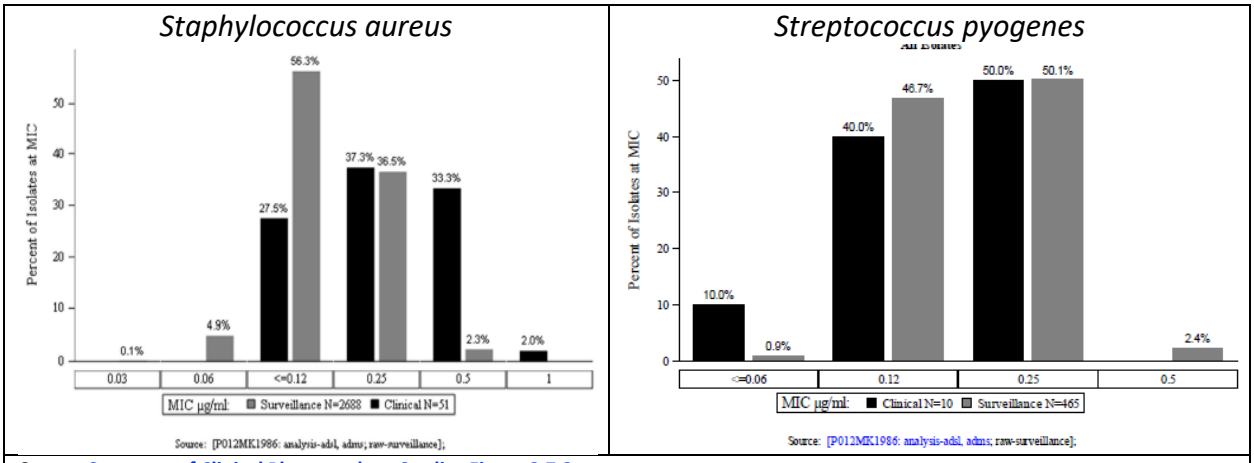
Tedizolid phosphate, an oxazolidinone class antibacterial prodrug, is an inhibitor of protein synthesis through interaction with the 50S subunit of the bacterial ribosome, preventing the initiation of translation by inhibiting the formation of the initiation complex. This clinical microbiology overview summarizes the marketing application for expanding the use of tedizolid phosphate from the current use in adult patients ≥ 18 years of age with ABSSSI to include use in adolescent patients 12 to < 18 years of age with ABSSSI.

4.3.1. Antimicrobial Spectrum of Activity

The activity of tedizolid from the STAR global surveillance program (2016 – 2018) showed that:

- Against 2688 *S. aureus* isolates, >99% were susceptible to tedizolid with MIC_{50} values ranging from 0.125 – 0.25 mcg/mL and MIC_{90} values of 0.25 mcg/mL. Against MRSA isolates, the tedizolid $MIC_{50/90}$ values were 0.12 mcg/mL and 0.25 mcg/mL, respectively.
- Against CoNS isolates, >98% were susceptible to tedizolid at MIC values ≤ 0.5 mcg/mL and MIC_{50} values of 0.12 mcg/mL and MIC_{90} values of 0.12 – 0.25 mcg/mL.
- Against 465 *S. pyogenes* isolates, 100% of isolates were susceptible to tedizolid with MIC_{50} values ranging from 0.12 – 0.25 mcg/mL and MIC_{90} values of 0.25 mcg/mL.
- The MIC frequency distributions of gram-positive baseline isolates from Study MK-1986-012 including *Staphylococci* spp. and *S. pyogenes* were comparable to gram-positive surveillance isolates. No notable differences in activity were observed in the US, Europe and other geographical regions.

Figure 1: Population Distribution of Tedizolid MICs for STAR Global Surveillance (2016 - 2018) and Study MK-1986-012 Clinical Isolates



Source: **Summary of Clinical Pharmacology Studies Figure 2.7.2.**

4.3.2. Animal Models of Infection

There were no new *in vivo* (animal) studies conducted in support of the adolescent ABSSSI indication.

4.3.3. Pharmacokinetics/Pharmacodynamics

No new formulation was developed for the adolescent ABSSSI program. The same dosage and formulation for adults (200 mg of tedizolid phosphate orally or IV infusion over 1 hour for 6 days) are proposed for adolescents (for further details see ***Section 6. Clinical Pharmacology***).

- The PK/PD driver associated with efficacy of tedizolid is the ratio of the free area under concentration curve to the minimum inhibitory concentration (*f*AUC/MIC).
- In various pre-clinical studies and animal studies, the *f*AUC/MIC ratio to achieve stasis in immunocompetent mice was approximately 3 given the susceptibility breakpoint MIC is 0.5 mcg/mL for *S. aureus* and *S. pyogenes*. Considering an 80% fraction bound, *f*AUC is calculated as 0.2 AUC. This would correspond to a total AUC/MIC ratio of approximately 15.
- Population PK modeling in adolescent patients with ABSSSI showed that there was 100% probability of target attainment (PTA) at an MIC value of 0.5 mcg/mL and 97% at an MIC of 1 mcg/mL after IV administration (Table 1). The PTA was 99.9% at an MIC value of 0.5 mcg/mL and 91.2% at an MIC of 1 mcg/mL after oral administration, indicating a high probability of PK/PD target achievement. Overall, tedizolid phosphate dosage of 200 mg IV and/or orally once daily predicts achievable exposures with a PTA of approximately 100% for MIC ≤ 0.5 mcg/mL in adolescent patients with ABSSSI.

Table 1: Percentage of adolescent patients with ABSSSI achieving a PK/PD target of fAUC/MIC =3 of tedizolid in plasma after IV and oral administration of 200 mg tedizolid phosphate once daily for 6 days

% of Adolescent ABSSSI Subjects Achieving PK/PD Target (fAUC/MIC =3)										
MIC (µg/mL)	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8
IV	100	100	100	100	100	100	97	46.5	2.1	0
Oral	100	100	100	100	99.9	99.9	91.2	28	0.3	0

ABSSI = acute bacterial skin and skin structure infections; *f*AUC = area under the concentration-time curve for free drug; MIC = minimum inhibitory concentrations; PK/PD = pharmacokinetic/pharmacodynamic
Source: [Ref.5.3.5.3.:0577KH]

4.3.4. Clinical Microbiology Efficacy Study Evaluation

Clinical and microbiological efficacy data in adolescent patients with ABSSSI (for details on study design and clinical results see ***Section 8. Statistical and Clinical and Evaluation***) showed that:

- Of the 120 adolescent participants enrolled, baseline specimens were collected for 83 participants (61 in the tedizolid group and 22 in the comparator group , ITT Analysis Set). Of these, 64 participants (48 in the tedizolid group and 16 in the comparator group) were included in the MITT Analysis Set.
- The distribution of baseline pathogens was similar and proportionately balanced between the tedizolid and comparator groups.
  - *S. aureus* was the most prevalent organism in both treatment groups in the MITT analysis set (41/48 (85.4%) in the tedizolid group and 14/16 [87.5%] in the comparator group). The *S. aureus* isolates consisted primarily of MSSA (35 in tedizolid group and 12 in the comparator group) whereas only 6% were MRSA (2 in tedizolid group and 1 in comparator group).
  - *S. pyogenes* was isolated from 9 in the tedizolid group (of whom 3 had a mixed infection with *S. aureus* [1 MRSA, 2 MSSA] isolated) and 2 [18%] in the comparator group).
  - Other baseline pathogens isolated included 2 isolates of *S. haemolyticus* (4.2%) and 1 *Peptoniphilus asaccharolyticus* isolate (2.1%), 1 *S. lugdunensis* (2.1%) and 1 *S. constellatus* (2.1%) all in the tedizolid group.
  - The majority of ABSSSIs in the tedizolid group (85.4%) and all in the comparator group were monomicrobial gram-positive infections. The remaining 15% in the tedizolid group were polymicrobial gram-positive infections. There were no mixed (gram-positive plus gram-negative) infections in either treatment group.
- The tedizolid MIC values for pathogens ranged from ≤ 0.06 to 1 mcg/mL in participants who received tedizolid in the study.
  - For *S. aureus* the $MIC_{50/90}$ values for tedizolid were 0.25/0.25 mcg/mL. Among *S. aureus* isolates, 98.2% were susceptible to tedizolid and only 1 isolate with an MIC 1 mcg/mL was intermediate according to FDA criteria. The participant in the tedizolid treatment group infected with the *S. aureus* isolate with an MIC of 1 mcg/mL was a clinical success and had a favorable microbiological response.

- For MRSA, clinical success rates were 100% in both tedizolid and comparator groups in the MITT analysis set. Favorable microbiological response rates were 100% in both the tedizolid and comparator groups
- For MSSA, clinical success rates were comparable in the tedizolid group (94.3%) compared with the comparator group (91.7%) in the MITT analysis set. Favorable microbiological response rates were 92% in the tedizolid group and 100% in the comparator group.
- For *S. pyogenes* the tedizolid $MIC_{50/90}$ values were 0.12/0.12 mcg/mL. All 11 (100%) *S. pyogenes* isolates were susceptible to tedizolid. Clinical success rates were 100% in both the tedizolid and comparator groups in both the MITT and ME analysis sets. Favorable microbiological response rates for tedizolid were 89% in the tedizolid group and 100% in the comparator group.
- Clinical success and favorable microbiological response rates were 100% for *P. asaccharolyticus, S. haemolyticus, S. lugdunensis* and *S. constellatus* in the tedizolid treatment group.
  - There were no instances of decreased susceptibility (>3-fold dilution increases in MIC), superinfections or new infection in both treatment groups

Microbiology Reviewer Comment: *There are no new organisms to add to Section 12.4 Microbiology (List 1 or List 2) of the labeling. There are no changes to the current tedizolid susceptibility interpretive criteria for S. aureus (including MRSA and MSSA) and S. pyogenes.*

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

The nonclinical review during the original tedizolid application found the drug safe for administration at clinical doses of 200mg oral and intravenous for 14 days. The rat and dog toxicology studies demonstrated that the major toxicities were hematopoietic (more pronounced in the rat and including decreased RBC, WBC, platelets and bone marrow hypocellularity), gastrointestinal, and injection site reactions (dog only). The summary review from 2014 notes that the systemic toxicities were dose and duration dependent, reversible, and occurred at tedizolid plasma exposures between four and ten times higher than the human exposure. At longer durations and higher exposures in the rate, toxicities to the liver (increased liver enzymes and hepatocellular centrilobular degeneration and atrophy), renal tubular degeneration, and reproductive organ degeneration and atrophy in both males and females were observed. Although juvenile toxicology studies were not submitted, the rat studies were conducted in an age group which would be adequate to assess the safety in the adolescent population. Skeletal muscles were not noted to be a target organ of toxicity.

6 Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology (Division of Infectious Diseases Pharmacology; OCP/DIDP) reviewed the clinical pharmacology information contained in sNDA 205435/S012 and 205436/S007. OCP's recommendations and comments on key review issues are summarized in the table below.

Table 2. Summary of OCP Recommendations and Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy assessment of SIVEXTRO (tedizolid phosphate) in adolescent patients with ABSSSI is extrapolated from adults, and supported by a Phase 3 randomized, single blind, multicenter, active-controlled trial to assess the safety and efficacy of IV to oral 6-Day SIVEXTRO compared with 10-Day comparator in pediatric patients 12 to <18 years with ABSSSI. Tedizolid PK assessed by population PK modeling showed a slightly higher AUC and Cmax in adolescent patients as compared to adults. No new safety concerns were identified in adolescent patients.
General Dosing Instructions	200 mg administered once daily orally or as an intravenous (IV) infusion over 1 hour for six days in adult and pediatric patients 12 years of age and older
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended based on intrinsic and extrinsic factors.
Labeling	The Applicant's proposed labeling required minor edits. The review team has specific content and formatting change recommendations that were communicated to the Applicant.

6.2. Summary of Clinical Pharmacology Assessment

The PK of tedizolid, the active metabolite of tedizolid phosphate, in adolescents were evaluated in one Phase 1 study under the original applications (NDA 205435/205436; Study P026) and one Phase 3 study in the current supplements (Study MK-1986-012).

In Study P026, tedizolid AUCs in adolescents with confirmed or suspected gram-positive bacterial infections were comparable to adult patients following single oral or IV administration of 200 mg SIVEXTRO. Cmax was 47% higher in adolescents as compared to adults receiving a single IV dose of tedizolid phosphate and comparable in adolescents and adults receiving a single oral dose of tedizolid phosphate. In Study MK-1986-012, tedizolid exposures were higher

in adolescent patients compared to adults following multiple dose administration of IV or oral SIVEXTRO (Cmax 3.15 vs. 2.04 mcg/mL, AUC_{24h} 28.9 vs. 21.2 mcg*h/mL). This increase in tedizolid exposure in adolescents was associated with an acceptable safety profile and is not considered clinically significant.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology profile of tedizolid phosphate in adults has been characterized and detailed in the original marketing application (NDA 205435/205436).

Table 3. General Pharmacology and Pharmacokinetic Characteristics

Mechanism of Action	The antibacterial activity of tedizolid is mediated by binding to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis.
QT Prolongation	In adults, tedizolid did not significantly affect heart rate, electrocardiogram morphology, PR, QRS, or QT interval following a therapeutic dose of 200 mg or supratherapeutic dose of 1200 mg.
Active Moiety	Tedizolid
Bioanalysis	Plasma samples in adolescent patients were assayed for tedizolid and tedizolid phosphate using validated LC-MS/MS assays.
Bioavailability	Similar to adults, the absolute bioavailability in adolescents is approximately 90% and no dosage adjustment is necessary between intravenous and oral administration.
Half-life	Approximately 12 hours
Pharmacokinetic Drug Interactions	SIVEXTRO (when administered orally) can increase the plasma concentrations of orally administered Breast Cancer Resistance Protein (BCRP) substrates.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of SIVEXTRO in adolescent patients is primarily based on extrapolation from adult patients by matching tedizolid exposures in adolescents to adults. The efficacy is also supported by a Phase 3 randomized, single blind, multicenter, active-controlled trial to assess the efficacy and safety of IV to oral 6-day SIVEXTRO compared with 10-day comparator in pediatric patients 12 to <18 years with ABSSSI. The primary objective of this Phase 3 trial was to evaluate the safety and tolerability of SIVEXTRO. The study was not powered for comparative inferential efficacy analysis. This study observed a high rate of clinical success and identified no new safety issues in adolescent ABSSSI patients treated with SIVEXTRO (See Section 8).

Multiple dose PK derived from Study MK-1986-012 showed tedizolid Cmax and AUC to be slightly higher in adolescent patients as compared to adult patients when PK data following IV and oral administration were combined (Table 4). When stratified by formulation, the increase in tedizolid Cmax and AUC in adolescent patients was less evident compared to adults (Table 5).

Table 4. Tedizolid Exposure Following Multiple IV and Oral Doses of 200 mg Daily for 6 Days

Tedizolid exposure after the last dose (200 mg once daily IV to oral for 6 days)	**Geometric Mean**		**Geometric Mean Ratio [90%CI]**
	[a]Adolescents	[b]Adults	
Cmax (mcg/mL)	3.15	2.04	1.54 [1.44-1.66]
AUC_{24h} (mcg*h/mL)	28.9	21.2	1.37 [1.28-1.45]
[a]Adolescents (n=89) from Phase 3 study (MK-1986-012) in adolescents with ABSSSI [b]ABSSSI adult patients (n=817) from Phase 2 and 3 studies (104, 112,113, 16099, 16121)			

Table 5. Tedizolid Exposure Following Multiple IV and Oral Doses of 200 mg Daily for 6 days; Stratified by Formulation

Tedizolid exposure after the last dose (200 mg once daily IV to oral for 6 days)		**Geometric Mean**	
		Oral (oral only or IV to oral)	**IV**
Cmax (mcg/mL)	Adolescents [a]	2.6	3.4
	Adults [b]	1.9	2.9
AUC_{24h} (mcg*h/mL)	Adolescents [a]	27.6	28.9
	Adults [b]	20.6	23.3
[a]Adolescents (n=89) from Phase 3 study (MK-1986-012) in adolescents with ABSSSI [b]ABSSSI adult patients (n=817) from Phase 2 and 3 studies (104,112,113, 16099, 16121)			

Based on the population PK model, body weight was found to a covariate that impacts tedizolid PK. The higher exposure in adolescents is thought to mainly be due to the lower body weight in adolescent patients compared to adult patients. The mean body weight was 80.7 kg and 59.5 kg for the ABSSSI adult patients and the adolescent patients included in this analysis, respectively.

See the Pharmacometrics review in Appendix 19.4 for a comparison of tedizolid exposure in adolescent patients stratified by quartile weight groups. It should also be noted that a smaller number of adolescent patients received SIVEXTRO as an oral only regimen as compared to adult patients. Of the 91 patients enrolled in Study MK-1986-012, five patients (5.5%) received only oral doses, 47 (51.6%) patients received only IV doses, and 39 (42.9%) switched from IV to oral doses. Nevertheless, slightly higher tedizolid exposure in adolescent patients compared to adult patients supports the extrapolation of SIVEXTRO efficacy from adults to adolescents.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

In the Phase 3 trial (MK-1986-012), adolescent patients received the approved adult dosage of 200 mg once daily orally or as an IV infusion over 1 hour for 6 days. Tedizolid exposures (AUC and Cmax) were slightly higher in pediatric patients 12 to <18 years of age following administration of IV or oral SIVEXTRO; however, this increase in exposure is not clinically significant given the acceptable safety profile in adolescent patients (See Section 8 for a more detailed review of clinical efficacy and safety). Further, probability of target attainment (PTA) analyses in adolescents suggest a high probability of antibacterial efficacy against clinically relevant gram-positive pathogens (See Appendix 19.4). These data support the recommendation to use the same dosage approved for adults in adolescents with ABSSSI.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

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Table 6: Listing of Clinical Trials Relevant to these sNDAs

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route/ treatment duration	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety					
Study 112 (submitted to support NDA)		Randomized, double blind, active-controlled, multicenter, noninferiority trial	200mg tedizolid phosphate (oral) daily x 6 days 600mg linezolid bid (oral) x 10 days	Primary: Noninferiority (NI) in the early clinical response rate at 48-72 hours in ITT population; responder afebrile with no spread of Lesion	ITT: Tedizolid phosphate: 332 Linezolid: 335 Safety: Tedizolid phosphate: 331 Linezolid: 335	Adults	81 sites in North America, Europe, and Latin America
Study 113 (submitted to support NDA)		Randomized, double blind, active-controlled, multicenter, noninferiority trial	200mg tedizolid phosphate (oral) daily x 6 days 600mg linezolid bid (oral) x 10 days	Noninferiority (NI) in the early clinical response rate at 48-72 hours in ITT population; responder 20% reduction in primary lesion	ITT: Tedizolid phosphate: 332 Linezolid: 334	Adults Tedizolid phosphate: one 17 y/o patient Linezolid: one 15 y/o patient	95 sites in the US, Europe South Africa, Australia/New Zealand, and Argentina
Study MK-1986-012		Randomized, investigator blinded, multicenter study	200 mg tedizolid phosphate iv to oral switch x 6 days Comparator x 10 days Comparators: vancomycin, linezolid (non-EU sites	Primary objective was to compare safety between tedizolid and comparator. Clinical response at the test of cure visit (Day 18-25) was	120 patients Tedizolid (n=91), comparator (21)	Adolescents 12 years <18 years	65 centers in 9 countries (7 in Europe plus the United States and South Africa).

			only), clindamycin, flucloxacillin, or cefazolin (administered IV) and/or linezolid (non-EU sites only), clindamycin, flucloxacillin, or cephalexin (administered orally)	assessed. Clinical successes were required to have resolution or near resolution of all related signs and symptoms such that no further antibacterial therapy was needed.			

7.2. Review Strategy

The review focuses on Study MK-1986-012, "Phase 3 Study of IV to Oral 6-Day Tedizolid Phosphate Compared with 10-Day Comparator in Subjects 12 to <18 Years with cSSTI." This study, submitted with these sNDAs, provided evidence of safety as well as efficacy in adolescent patients with ABSSSI. The efficacy of SIVEXTRO in adolescent patients is primarily based on extrapolation from findings in adult patients by matching tedizolid exposures in adolescents to exposures in adults.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. MK-1986-012: Study Design

Study Design

Study MK-1986-012 is a randomized, evaluator blinded, multicenter, Phase 3 study of tedizolid phosphate (200 mg administered IV and/or orally once a day) versus comparator therapy (administered IV and/or orally for 10 days) for the treatment of suspected or documented gram-positive ABSSSI in participants 12 to less than 18 years of age. Both the investigators and patients were unblinded in the trial, however, assessments of the primary and secondary endpoints were performed by a blinded evaluator.

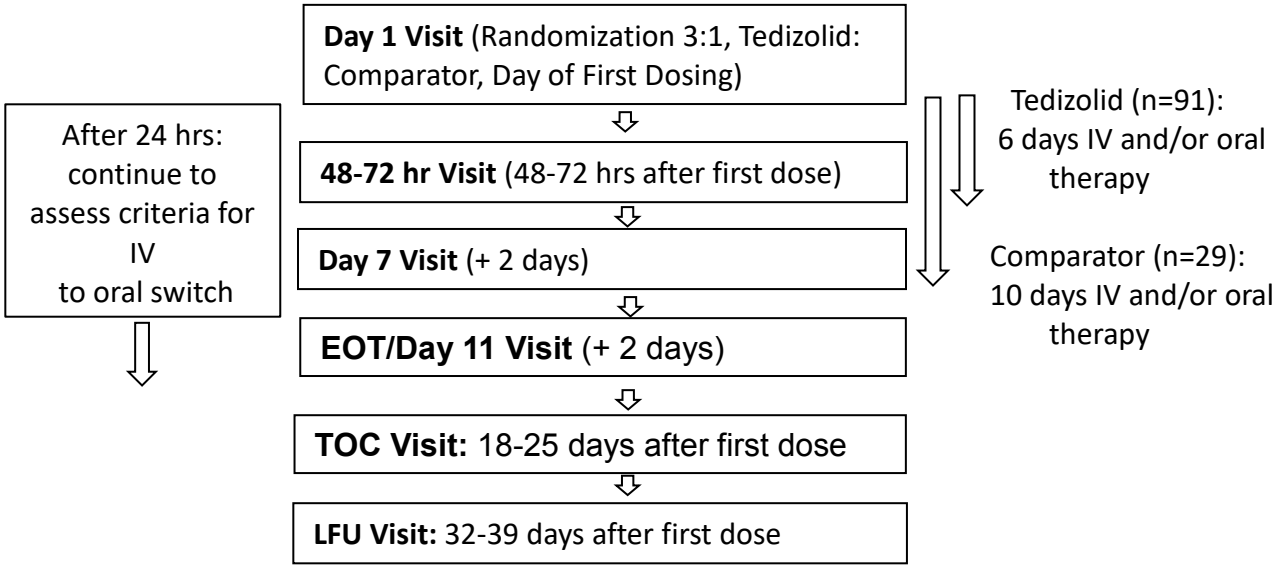
The study planned to randomize 120 patients with at least 86 patients treated with tedizolid and included in the Safety Analysis Set. Patients were randomized in a 3:1 ratio to receive either tedizolid or comparator therapy. The randomization was stratified by geographic region (North America, Europe and South Africa) using interactive response technology. IV comparators included vancomycin, linezolid (except in EU), clindamycin, flucloxacillin and cefazolin. Oral comparators included linezolid (except in EU), clindamycin, flucloxacillin and cephalexin. The selection, dose, and dose frequency of these antibacterials was determined by the study site.

Following screening on Day -1 or Day 1, patients received study drug on the Day 1 visit and subsequently completed five follow-up visits: a 48-72 hour visit, Day 7 visit, End-of-Treatment Visit (EOT, Day 11), Test-of-Cure visit (TOC, 18-25 days after first dose) and Late Follow-up Visit (LFU, 32-39 days after first dose) as shown in **Figure 2**. After receiving oral or IV therapy for 24 or more hours, patients were assessed for a possible IV-to-oral switch using pre-defined criteria.

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

- Primary skin lesion did not increase in length or width from baseline
- Last temperature was <37.7° C
- Signs and symptoms of the primary ABSSSI site had not worsened with at least 1 site improved from baseline.

Figure 2: Study Design



Note: All patients received at least 24 hrs of IV therapy with the exception of 7 patients (5 in tedizolid arm, 2 in comparator arm) who received oral therapy only.

Source: Reviewer Figure

Study Endpoints

The primary efficacy endpoint was clinical response (per blinded investigator's assessment) at the TOC visit. The secondary efficacy endpoints were early clinical response at 48-72 hours and clinical response (per blinded investigator's assessment) at the EOT visit. For the early clinical response endpoint, patients with a 20% or greater reduction in baseline lesion area were evaluated as a success/responder, those with less than a 20% reduction in baseline area were evaluated as a failure/nonresponder and those with missing lesion area data were evaluated as indeterminate. For the clinical response endpoints at EOT/TOC, patients were evaluated as either a clinical success, clinical failure or indeterminate according to the criteria shown in **Table 7**.

Reviewer Comments: T*he ABSSSI Guidance recommends that noninferiority is assessed based on early clinical response at 48-72 hours (the recommended primary endpoint). An NI margin of 10% is generally recommended for testing this endpoint.*

Patients whose disease was progressing or who received rescue or prohibited concomitant therapy prior to the EOT visit were considered as clinical failures at the EOT and TOC visits. Patients who were clinical failures at the EOT visit or who had relapsed between the EOT and TOC visits and received additional prohibited concomitant therapy were considered as clinical failures at the TOC visit. Patients assessed as clinical failures at any time during the study were

considered as clinical failures at the TOC visit. Patients who were indeterminate at the EOT visit were considered as non-successes (failures or indeterminates) at the TOC visit.

As shown in **Table 8**, patients who were clinical successes at TOC were later assessed at the LFU visit (32-39 days after first dose) and classified as either a sustained clinical success (no new signs or symptoms of the primary cSSTI after TOC), a clinical relapse (new or worsening signs and symptoms of the primary cSSTI after TOC) or as an indeterminate (study data are not available for the evaluation of clinical relapse or sustained clinical success). Note that if the LFU visit occurred via telephone contact, the evaluation may be based on the patient's report.

Additional efficacy endpoints included the following:

- Microbiological response (defined below)
- Change from baseline in lesion size, signs and symptoms, and regional or systemic signs
- Clinical success and per-pathogen clinical success (per blinded investigator's assessment) at the TOC Visit
- Subject Reported Outcome assessment (pain)

Table 7: Blinded Investigator's Assessment of Clinical Response Definitions (EOT and TOC)

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 so no further antibiotic therapy is required for the treatment of the primary lesion
Clinical Failure	Any of the following: • Requires additional antibiotic therapy for treatment of the primary lesion • Unplanned major surgical intervention required due to failure of study drug (i.e., amputation) • Developed osteomyelitis after baseline • Persistent gram-positive pathogen bacteremia • Treatment-emergent AE leading to discontinuation of study drug and subject required additional antibiotic therapy to treat the infection under study

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

Table 8: Blinded Investigator Assessment of Clinical Relapse Definitions (LFU)

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

Source: Adapted from Applicant Table 5 of SAP

Microbiological samples were required at baseline for all patients and required post-baseline in patients with no improvement in the primary lesion where the primary lesion was easily accessible. Microbiological response was determined based on data from the central microbiology laboratory and the blinded investigator's assessment of clinical response. According to the criteria shown in **Table 9**, patients with at least one baseline pathogen having persistence or presumed persistence had a microbiological response of 'unfavorable' while patients with all baseline pathogens having eradication or presumed eradication had a microbiological response of 'favorable.' As shown in **Table 10**, the overall microbiologic response was defined using the microbiologic response at the EOT and TOC Visits.

Table 9: Pathogen Level Microbiological Response Definitions

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

Source: Adapted from Applicant Table 6 of SAP
Note: Response is per pathogen. The per-patient response is based on all pathogens present at baseline for that patient.

Table 10: Subject Level Microbiological Response

EOT Visit	TOC Visit	Microbiologic Response
Favorable	Favorable	Favorable
Favorable	Unfavorable	Unfavorable
Favorable	Indeterminate	Indeterminate
Unfavorable	Favorable	Favorable
Unfavorable	Unfavorable	Unfavorable
Unfavorable	Indeterminate	Unfavorable
Indeterminate	Favorable	Favorable
Indeterminate	Unfavorable	Unfavorable
Indeterminate	Indeterminate	Indeterminate

Source: Adapted from Applicant Table 7 of SAP

Statistical Analysis Plan

Analysis Sets

The Applicant defined the follow analysis sets. The intent-to-treat (ITT) and clinically evaluable at TOC (CE-TOC) sets were the primary analysis sets used in the efficacy evaluation.

- ITT- all randomized patients. (Treatment assignment based on the study treatment the patient was randomized to).
- Safety - all patients who received any amount of study drug. (Treatment assignment based on the study treatment the patient received).
- Microbiological ITT (Micro-ITT)- all ITT patients with a baseline gram-positive bacterial pathogen known to cause complicated skin and soft-tissue infections (cSSTI).
- CE-TOC- all ITT patients who:
  - received at least 1 full dose of study treatment
  - complied with the study protocol with no important deviations
  - completed EOT and TOC assessments (unless assessed as failures at any time point before the EOT Visit)
  - had no concomitant systemic antibacterial therapy that was potentially effective against the baseline gram-negative pathogen except adjunction azithromycin and/or metronidazole in subjects with wound infections and ≤ 24 hours of surgical prophylaxis systemic antibiotic therapy.
- ME- All patients from the Micro-ITT analysis set who were also in the CE-TOC Analysis set

Reviewer Comment: *We generally recommend that analyses are performed using ITT-based rather than evaluable analysis populations. Analyses in evaluable populations may be more subject to biases since they may involve post-baseline exclusions related to the effect of the study treatment.*

Statistical Methodology

For the primary efficacy endpoint, treatment differences in clinical success rates (per blinded investigator's assessment) at TOC in the ITT and CE-TOC populations were estimated using a two-sided 95% CI based on the unstratified method of Miettinen and Nurminen. Patients with any missing information for the outcome (e.g. assessment of signs and symptoms) were assigned a response of indeterminate. For the ITT analysis, indeterminates were included in the denominator and thus considered as clinical failures. By definition, patients with indeterminate responses were excluded from CE-TOC analysis.

For the secondary efficacy endpoints, analyses of the differences in early clinical response rates at 48-72 hours and clinical success rates (per blinded investigator's assessment) at EOT were based on the same methodology described for the primary efficacy endpoint. Note that the early clinical response rate endpoint was only assessed in the ITT population whereas the

clinical success rate endpoints at EOT and TOC were assessed in both the ITT and CE-EOT populations.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) was used to review safety data including AEs, vital signs, physical examinations, and laboratory data when one third and two thirds of enrollment was complete.

Sample Size Considerations

The original planned sample size for this study, conducted to fulfill PMR #2159-1, was 162 patients (109 tedizolid evaluable). This study was not powered for inferential statistics because the primary objective was safety. It was rather powered to adequately detect adverse events occurring at 10% and 2%. Due to a slower than expected rate of study enrollment in conducting this trial, the Applicant proposed to decrease the sample size to 120 total enrolled patients (86 tedizolid evaluable). This change in sample size, along with a change in the study completion date from June 2018 to February 2019, was requested on November 30, 2017 and was agreed to by the Agency during a meeting held on January 19, 2018. The Applicant indicated that with 86 tedizolid evaluable patients, the study would have an 82% probability of detecting at least one adverse event with a true event rate of 2%.[4]

Reviewer Comments: *The timing involved in deciding to stop a trial early could potentially lead to biases. Although sponsors are assumed to be blinded under the protocol, they could have knowledge of study results, especially in an investigator unblinded trial. We note there were 90 patients enrolled prior to Nov. 30, 2017 when the request was made to stop the study early. Results appeared to be favorable in these patients with clinical success rates at TOC of 64/66 (97.0%) in the tedizolid arm versus 22/24 (91.7%) in the comparator arm.*

Protocol Amendments

The Applicant made six amendments to the original protocol which was finalized on Aug. 13, 2014. The amendments shown below were all made after the start of the study (date first patient enrolled) which was September 2015. The completion date of the study was February 2019.

Amendment 3 (finalized Apr. 12, 2016)

- "IV to oral" therapy is changed to "IV and/or oral" with at least 50% of patients receiving at least 24 hours of IV therapy
- Modification of lesion size requirement in the inclusion criteria: instead of requiring a minimal lesion area of 75 cm^2 (or less, when scaled to body surface area, BSA), a minimal lesion length of 4 cm is the longest dimension now required.
  Since the minimal lesion area of 75 cm^2 was reduced, additional severity criteria were

[4] Schoenfeld D. Statistical considerations for pilot studies. Int. J. Radiation Oncology Biol. Phys Vol 6: 371-374, 1980

added for inclusion.

Amendment 4 (finalized Nov. 4, 2016)

- Added limitation that linezolid (IV or oral) is allowed as a comparator outside of Europe only
- Exclusion Criterion #12 was updated to topical antibacterial ointments or creams applied to and remaining on the lesion prior to randomization for a duration of ≥ 24 hrs.), except for antibiotic/antiseptic-coated dressings applied to clean postsurgical wounds.
  Exclusion Criterion #2 was modified to exclude patients with concomitant severe acute bacterial infection at another site not including a secondary cSSTI lesion (e.g. septic arthritis, endocarditis, osteomyelitis) which often require prolonged durations of antibiotic therapy that are not permitted in the study.
- Protocol change specified that in the absence of rescue treatment (and presence of ongoing consent), efficacy should be assessed even if the patient is discontinued from study drug. This change was made to minimize the potential for missing assessments of efficacy.

Amendment 6 (finalized Feb. 26, 2018)

- Changed the number of patients planned to be enrolled from 162 to 120 to expedite study completion and provide more timely data to guide treatment for ABSSSI in children.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the trial was conducted in the compliance with Good Clinical Practices (GCPs).

Financial Disclosure

The Applicant certified that the clinical investigators had not entered into any financial arrangements whereby the value of the compensation could affect the outcome of the trial. None of the investigators had a proprietary interest in the product, had significant equity in the Applicant, or had received significant payments of other sorts as defined in 21 CFR part 54.

Patient Disposition

The study randomized 121 patients and enrolled 120 patients who comprised the ITT population. Of the 120 ITT patients, all patients received at least 1 dose of study medication (91 in tedizolid arm, 29 in comparator arm) and were included in the Safety population. Nearly 97% of ITT/Safety patients completed study treatment and completed the study as per protocol. The few remaining patients (3% in each treatment arm) discontinued both study treatment and the study itself. The three discontinuations in the tedizolid arm were due to an adverse event, a patient withdrawal and a gram-negative infection, respectively. The

discontinuation in the comparator arm was due to other reasons (i.e. patient met criteria for oral switch but the isolated pathogen was resistant to the available oral antibacterial drugs).

The number of patients observed in each of the defined analysis populations and the reasons for exclusion from each of the analysis populations is shown in the table below. The majority of those excluded from the Micro-ITT were due to no gram-positive pathogen being identified at baseline. Three patients with a gram-negative isolate at baseline (2 in the tedizolid arm, 1 in the comparator arm) were also excluded from the Micro-ITT population as well as the evaluable populations. The three patients who discontinued the study were also excluded from the evaluable populations.

Table 11: Analysis Populations and Reasons for Exclusion

Analysis Set	Tedizolid N (%)	Comparator N (%)	Total N (%)
ITT/Safety	**91 (100%)**	**29 (100%)**	**120 (100%)**
Micro-ITT	**48 (53%)**	**16 (55%)**	**64 (53%)**
Not in Micro-ITT	43 (47%)	13 (45%)	56 (47%)
Gram-negative Isolate	2 (2%)	1 (3%)	3 (3%)
No Gram-positive Pathogen	41 (45%)	12 (41%)	53 (44%)
CE-EOT	**87 (96%)**	**27 (93%)**	**114 (95%)**
Not in CE-EOT	4 (4%)	2 (7%)	6 (5%)
Effective concomitant therapy prior to EOT	1 (1%)	0	1 (1%)
Gram-negative Isolate	2 (2%)	1 (3%)	3 (3%)
Insufficient clinical evaluation	1 (1%)	1 (3%)	2 (2%)
CE-TOC	**87 (96%)**	**27 (93%)**	**114 (95%)**
Not in CE-TOC	4 (4%)	2 (7%)	6 (5%)
Gram-negative Isolate	2 (2%)	1 (3%)	3 (3%)
Insufficient clinical evaluation	2 (2%)	1 (3%)	3 (3%)
ME	**46 (51%)**	**16 (55%)**	**62 (52%)**
Not in ME	45 (49%)	14 (45%)	58 (48%)
Not in CE-TOC	2 (2%)	0	2 (2%)
Not in Micro-ITT	43 (47%)	13 (45%)	56 (47%)

Source: Partially adapted from Applicant Table 14.1-4 in CSR

Reviewer Comment: *There was one patient in the tedizolid arm who was randomized in error prior to obtaining consent from both parents. This patient was not included in the ITT population (or any other analysis population). No study-related procedures were conducted on this patient. Given that this trial was not fully blinded it is not clear if treatment assignment might have led to the decision to not give consent to the trial.*

Protocol Deviations

As shown in **Table 12,** there were 46 important protocol deviations reported in 31 (26%) of ITT patients, 20 (22%) of patients in the tedizolid arm and 11 (38%) of patients in the comparator arm. Most of the observed deviations fell into the category of 'trial procedures' and were

related to assessments or visits being performed outside of the planned window or to assessments not being performed (primarily hematology, blood chemistry or pregnancy).

Table 12: Summary of Notable Protocol Deviations

Deviation	Tedizolid (N=91) n (%)	Comparator (N=29) n (%)	Total (N=120) n (%)
Number of patients with at least one notable deviation	**20 (22%)**	**11 (38%)**	**31 (26%)**
Reasons other than trial procedures	**1 (1%)**	**2 (7%)**	**3 (3%)**
Informed Consent (wrong version used)	1 (1%)	0	1 (1%)
Prohibited Medication Taken During Trial	0	1 (3%)	1 (1%)
Did not receive full course of therapy, not assessed a as a clinical success at EOT or TOC	0	1 (3%)	1 (1%)
Reasons due to trial procedures	**19 (21%)**	**10 (34%)**	**29 (24%)**
Missing cSSTI site specimen at screening	1 (1%)	0	1 (1%)
Failure to complete pregnancy test prior to randomization[1]	2 (2%)	1 (3%)	3 (3%)
Missed the complete panel of hematology prior to randomization	5 (5%)	1 (3%)	6 (5%)
48-72 hour Visit performed outside of window	3 (3%)	1 (3%)	4 (3%)
Lesion measurement at 48-72 hour visit performed outside of window	3 (3%)	2 (7%)	5 (4%)
EOT Visit performed outside of window	4 (4%)	1 (3%)	5 (4%)
Missed assessment of clinical response at EOT	0	1 (3%)	1 (1%)
Failure to complete pregnancy test prior to EOT Visit[2]	6 (7%)	2 (7%)	8 (7%)
TOC Visit performed outside of window	3 (3%)	1 (3%)	4 (3%)
Other[3]	0	4 (14%)	4 (3%)

Source: Adapted from Applicant Table 10-1 in CSR

1- No pregnancy was reported during the study or follow-up period among these 3 patients.

2- No pregnancy was reported during the study or follow-up period among these 8 patients.

3- Other reasons included missing the complete panel of blood chemistry prior to randomization, missing complete panel of hematology and blood chemistry at post-baseline visits, and missing all safety laboratory tests.

Note: Patients may have protocol deviations for more than one reason

***Reviewer Comments**: In this trial that is not fully blinded, it is not clear why there was this difference in protocol violations. It could be that investigators and/or patients followed the protocol more closely for those assigned to the test arm. Additionally, treatment differences in the number of protocol deviations may have been influenced by differences in the nature of the study therapy. The comparator therapy was administered over a longer time period and involved a larger number of study drug administrations. The comparator therapy was also more complex, consisting of several different IV and oral therapies with more variable daily dosing*

(e.g. QD, BID, TID, QID). The regimen in the tedizolid arm was easier to administer with patients receiving 200 mg of tedizolid IV and/or oral once a day.

Demographic Characteristics

Demographic characteristics in the ITT population are shown below. Patients were mostly white (87%), male (63%) or from European sites (78%). The mean age of patients in the study was 14.4 years. Patients in the two treatment groups were generally well balanced according to sex, age, race, ethnicity and geographic region. The study randomization was stratified by geographic region to ensure balance for that variable.

Table 13: Demographic characteristics of the ITT Population

Parameters	Tedizolid (N=91) n (%)	Comparator (N=29) n (%)	Total (N=120) n (%)
Sex			
Male	58 (64%)	17 (59%)	75 (63%)
Female	33 (36%)	12 (41%)	45 (38%)
Age			
Mean years (SD)	14.4 (1.7)	14.4 (2.0)	14.4 (1.7)
Median (years)	15	15	15
Min, max (years)	12, 17	12, 17	12, 17
Age Group			
12-14 years	43 (47%)	14 (48%)	57 (48%)
15-17 years	48 (53%)	15 (52%)	63 (53%)
Race			
White	80 (88%)	24 (83%)	104 (87%)
Black or African American	11 (12%)	4 (14%)	15 (13%)
Asian	0	1 (3%)	1 (1%)
Ethnicity			
Hispanic or Latino	4 (4%)	1 (3%)	5 (4%)
Not Hispanic or Latino	86 (95%)	28 (97%)	114 (95%)
Unknown	1 (1%)	0	1 (1%)
Geographic Region			
North America	8 (9%)	2 (7%)	10 (8%)
Europe	71 (78%)	23 (79%)	94 (78%)
South Africa	12 (13%)	4 (14%)	16 (13%)

Source: Partially Adapted from Applicant Table 10-3 in CSR

Other Baseline Characteristics

Table 14 shows other baseline characteristics of the primary efficacy population. There were some treatment imbalances in clinically important parameters as would be expected given the small number of patients in the comparator arm. For the infection type parameter, the tedizolid arm included a smaller percentage of patients with wound infections and a greater

percentage of patients with cellulitis/erysipelas and major cutaneous abscesses. The tedizolid arm also included a slightly greater percentage of patients who were hospitalized on Day 1 or had fever at baseline. The mean (and median) lesion size was also greater in the tedizolid arm, with a higher percentage of patients having lesions ≥ 300cm^2 and a lower percentage having lesions < 75 cm^2. Note that protocol amendment #3 reduced the requirement for baseline lesion size from a minimum of 75 cm^2 (or less, when scaled to body surface area), to a minimal lesion length of 4 cm in the longest dimension.

The degree of severity of signs and symptoms at baseline in the ITT population was also compared. For the majority of signs and symptoms, there was a greater percentage of patients in the tedizolid arm with severe signs and symptoms. This was most pronounced for 'pain or tenderness/tenderness of palpation' where 60% of patients in the tedizolid fell into the 'severe' category versus 38% of patients in the comparator arm. There were also notable differences for the symptom of 'localized warmth' with 45% of patients having severe localized warmth versus 28% in the comparator arm.

Table 14: Other baseline characteristics of the primary efficacy analysis (ITT Population)

Other Parameters	Tedizolid (N=91) n (%)	Comparator (N=29) n (%)	Total (N=120) n (%)
Type of Infection			
Cellulitis/Erysipelas	38 (42%)	10 (34%)	48 (40%)
Major Cutaneous Abscess	40 (44%)	11 (38%)	51 (43%)
Wound Infection	13 (14%)	8 (28%)	21 (18%)
Fever at Baseline			
Yes	59 (65%)	15 (52%)	74 (62%)
No	32 (35%)	14 (48%)	46 (38%)
Hospitalization at Day 1			
Yes	85 (93%)	25 (86%)	110 (92%)
No	6 (7%)	4 (14%)	10 (8%)
Lesion Surface Area (cm^2)			
Mean (SD)	135.4 (158.7)	83.2 (48.6)	122,8 (141.8)
Median	85.4	78.0	82.1
Min, Max	14, 978	16, 210	14, 978
Lesion Surface Area (cm^2)			
< 75 cm^2	29 (32%)	14 (48%)	43 (36%)
≥ 75 to < 150 cm^2	43 (47%)	11 (38%)	54 (45%)
≥ 150 to <300 cm^2	12 (13%)	4 (14%)	16 (13%)
≥ 300 cm^2	7 (8%)	0	7 (6%)
Major Baseline Pathogen[1]	N=48	N=16	N=64
Staphylococcus aureus	41 (85%)	14 (88%)	55 (86%)
MRSA	2 (4%)	1 (6%)	3 (5%)
MSSA	35 (73%)	12 (75%)	47 (73%)
Streptococcus pyogenes	9 (19%)	2 (13%)	11 (17%)

Source: Partially Adapted from Table 10-3 and Table 14.1-20 in CSR
1- Percentages are based on the Micro-IITT population which included only those ITT patients who had ABSSSI due to validated gram positive pathogen with no gram negative pathogens identified at baseline. Note that patients may have more than one pathogen at baseline

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment and Comparator Therapies

The treatment and comparator therapies received are described in **Table 15**. Approximately 95% and 93% of ITT patients in the tedizolid and comparator arms received IV therapy. The percentage of ITT patients who switched from IV to oral therapy was smaller in the tedizolid arm, 43% versus 62%. The timing of the switch tended to occur later in the comparator arm. The median number of days on IV before oral switch was 3 days in the tedizolid arm versus 4.5 days in the comparator arm.

Treatment comparisons by the days on treatment and number of administrations are also shown in this table. The mean number of days on treatment was 5.9 days (4.4 days IV, 3.5 days oral) for the tedizolid arm versus 9.8 days (6.1 days IV, 6.7 days oral) in the comparator arm. Approximately 1% of patients in the tedizolid arm received 8 or more doses of study drug versus 97% of patients in the comparator arm. These differences were likely related to the planned duration of treatment (6 days for tedizolid versus 10 days for the comparator) as well as the more frequent dosing in the comparator arm (QD in the tedizolid arm versus mostly BID or TID in the comparator arm).

Table 15: Treatment and Comparator Therapies

	Tedizolid (N=91)	**Comparator (N=29)**
Category of Therapy		
Oral Only Therapy	5 (5%)	2 (7%)
IV Therapy	86 (95%)	27 (93%)
IV Only Therapy	47 (52%)	9 (31%)
IV to Oral Switch, n (%)	39 (43%)	18 (62%)
Switch ≤ 3 days	26 (29%)	6 (21%)
Switch ≥ 4 days	13 (14%)	12 (41%)
Days on IV before Oral Switch (median)	3 days	4.5 days
Days on Treatment[1]		
Treatment	**n=91**	**n=29**
Mean (SD)	5.9 (0.8)	9.8 (1.8)
Median (Min, Max)	6 (1,8)	10 (3, 11)
IV treatment	**n=86**	**n=27**
Mean (SD)	4.4 (1.7)	6.1 (3.0)
Median (Min, Max)	6 (1,7)	6 (2, 11)
Oral treatment	**n=44**	**n=20**
Mean (SD)	3.5 (1.1)	6.7 (2.1)

Median (Min, Max)	3 (2,6)	7 (3, 10)
Number of Administrations		
Treatment	**n=91**	**n=29**
1-2 doses	3 (3%)	0
3-4 doses	0	1 (3%)
5-7 doses	87 (96%)	0
8-11 doses	1 (1%)	1 (3%)
12-16 doses	0	4 (14%)
> 16 doses	0	23 (79%)
IV treatment	**n=86**	**n=27**
1-2 doses	12 (13%)	0
3-4 doses	29 (32%)	6 (21%)
5-7 doses	45 (49%)	3 (10%)
8-11 doses	0	3 (10%)
12-16 doses	0	7 (24%)
> 16 doses	0	8 (28%)
Oral treatment	**n=44**	**n=20**
1-2 doses	4 (4%)	0
3-4 doses	33 (36%)	1 (3%)
5-7 doses	7 (8%)	1 (3%)
8-11 doses	0	3 (10%)
12-16 doses	0	5 (17%)
> 16 doses	0	10 (34%)

Source: Partially Adapted from Applicant Table 10-4
1- Calculated as (last dose date – first dose date) + 1

Table 16 provides a summary of the antibacterial drugs used by the 29 patients in the comparator arm. Two patients received oral therapy only while the remaining 27 patients (93%) received IV therapy. Among these 27 patients, 11 received cefazolin IV , 8 received vancomycin IV, 4 received linezolid IV and 4 received clindamycin IV. As indicated above, a relatively large percentage of patients who received cefazolin IV did not switch to oral therapy.

Table 16: Summary of Antibiotics used in the Comparator Arm (ITT Population)

Therapy Received	**Comparator (N=29) n (%)**
Cephalexin Oral Oral only	**1 (3%)**
Linezolid Oral Oral only	**1 (3%)**
Cefazolin IV	**11 (38%)**
IV only	7 (64%)
IV to oral switch (cefazolin IV to oral cephalexin or clindamycin)	4 (36%)
Vancomycin IV	**8 (28%)**

IV only	2 (25%)
IV to oral switch (vancomycin IV to oral flucloxacillin, cephalexin or clindamycin)	6 (75%)
Linezolid IV	**4 (14%)**
IV only	0 (0%)
IV to oral switch (linezolid IV to oral linezolid)	4 (100%)
Clindamycin IV	**4 (14%)**
IV only	0 (0%)
IV to oral switch (clindamycin IV to oral clindamycin)	4 (100%)

Source: Reviewer Table

Table 17 provides a listing of the IV and oral therapy received by the 29 patients in the comparator arm, including the number of doses (days) of therapy (IV and oral) received as well as the number of days on therapy (IV and oral). This table shows a high degree of variability with respect to the combination of IV and oral antibacterial drugs received as well as the prescribed dosing regimen (dose, frequency and duration). Although the types of antibacterial drugs selected were mostly consistent within each study site, the dosing regimen varied according to the discretion of the investigator. The duration of IV versus oral therapy also appeared to vary by site and/or the antibacterial drug selected for that site. Site 404, for example, included a relatively large percentage of patients who received IV therapy with no oral switch. All of these patients received cefazolin.

Reviewer Comments: *The unblinded study design could have had some influence on the antibacterial drug used or the planned dosing regimen. Note that the antibacterial drug and dosing regimen were not pre-specified in the comparator arm. The investigator could change the planned dosing frequency even during the course of therapy. However, limitations in standardization did not appear to substantially affect overall findings of efficacy. The two patients in the comparator arm who were counted as failures in the primary analysis were Patient* (b) (6) *(clinical failure) who received 10 days of therapy (100% compliance) and Patient (indeterminate) who was withdrawn by the investigator after receiving 2 days of treatment due to having a resistant pathogen isolated.*

Table 17: Summary Listing of 29 Patients on Comparator Regimen

Patient ID	IV Therapy	# IV doses (days of therapy)	Oral Therapy	# oral doses (days of therapy)	# doses (days of therapy)	# days on therapy (IV/oral)[1]
(b) (6)	None	0 (0)	250mg cephalexin QID	40 (10)	40 (10)	10 (0/10)
	None	0 (0)	600mg linezolid BID	20 (10)	20 (10)	10 (0/10)
	600mg linezolid BID	3 (1.5)	600mg linezolid BID	10 (5)	13 (6.5)	7 (2/5)
	600mg linezolid BID	3 (1.5)	600mg linezolid BID	17 (8.5)	20 (10)	11 (3/9)
	600mg linezolid BID	3 (1.5)	600mg linezolid BID	18 (9.0)	21 (10.5)	11 (2/9)
	600mg linezolid QD	3 (3)	600mg linezolid QD	7 (7)	10 (10)	10 (3/7)
	1g vancomycin QD	10 (10)	500mg flucloxacillin TID	15 (5)	25 (15)[2]	11 (6/6)
	500mg vancomycin BID	10 (5)	500mg flucloxacillin TID	14 (4.7)	24 (9.7)	10 (6/5)
	500mg vancomycin BID	6 (3)	500mg cephalexin TID	21 (7)	27 (10)	11 (4/8)
	1g vancomycin BID	6 (3)	500mg cephalexin TID	21 (7)	27 (10)	11 (4/8)
	1g vancomycin BID	4 (2)	1.5g cephalexin BID	16 (8)	20 (10)	10 (2/8)
	300mg clindamycin TID	13 (4.3)	300mg clindamycin TID	17 (5.7)	30 (10)	11 (5/7)
	1g vancomycin BID	4 (2)	none	0 (0)	4 (2)	3 (3/0)
	1g cefazolin TID	21 (7)	500mg cephalexin TID	9 (3)	30 (10)	11 (8/4)
	1g cefazolin TID	20 (6.7)	500mg cephalexin QD	3 (3)	23 (9.7)	10 (8/3)
	1g cefazolin TID	30 (10)	none	0 (0)	30 (10)	11 (11/0)
	1g cefazolin TID	29 (9.7)	none	0 (0)	29 (9.7)	11 (11/0)
	1g cefazolin BID	13 (6.5)	none	0 (0)	13 (6.5)	7 (7/0)
	1g cefazolin BID	13 (6.5)	none	0 (0)	13 (6.5)	7 (7/0)
	1g cefazolin BID	15 (7.5)	none	0 (0)	15 (7.5)	8 (8/0)
	1g cefazolin BID	19 (9.5)	none	0 (0)	19 (9.5)	10 (10/0)
	1g vancomycin BID	20 (10)	none	0 (0)	20 (10)	11 (11/0)
	1275mg cefazolin TID	19 (6.3)	500mg cephalexin QID	15 (3.8)	34 (10.1)	10 (7/4)
	750mg cefazolin TID	15 (5)	300mg clindamycin BID	10 (5)	25 (10)	11 (6/6)
	1.5g cefazolin TID	30 (10)	none	0 (0)	30 (10)	11 (11/0)
	600mg clindamycin TID	7 (2.3)	600mg clindamycin TID	22 (7.3)	29 (9.7)	10 (3/8)
	600mg clindamycin TID	10 (3.3)	300mg clindamycin TID	20 (6.7)	30 (10)	10 (4/7)
	600mg clindamycin TID	15 (5)	600mg clindamycin TID	19 (6.3)	34 (11.3)[3]	11 (6/6)
	1g vancomycin BID	12 (6)	300mg clindamycin QID	13 (3.3)	25 (9.3)	10 (7/4)

Source: Reviewer Table

1- Calculated as (last dose date – first dose date) + 1

2- Patient (b) (6) was recorded as receiving 1g vancomycin QD IV therapy from Day 1 to Day 6 but the investigator administered this therapy more frequently over this period (BID dosing).

3- Patient (b) (6) was recorded as receiving 600mg TID oral therapy from Day 6 to Day 11 but the investigator administered this therapy more frequently (QID dosing).

Treatment Compliance

Treatment compliance was calculated based on the percent of actual doses taken divided by the expected number of doses. In the tedizolid arm, approximately 96% of patients were 100% compliant with 97% of patients receiving at least 80% of the planned dosing.

Due to the longer duration and variable nature of the comparator treatment in which investigators had the flexibility of changing patient dosing, compliance as reported in the study report was substantially lower in the comparator arm. Approximately 41% of patients in the comparator arm were 100% compliant with 83% of patients receiving at least 80% of the planned dosing. The percentage of patients in the comparator arm with greater than 100% compliance (defined by the Applicant as receiving more than expected number of doses) was 24%.

Reviewer Comments: *The treatment compliance information on the comparator as reported by the Applicant should be viewed with caution. This is an unblinded trial with the selection, dose, and dose frequency of the comparator determined by the study* site. *It might not be appropriate to consider changes to the comparator as lack of compliance. In the comparator arm, three patients who received less than the protocol specified 10 days of therapy were from a single site (site 404). The site investigator stopped drug administration in these patients after the primary ABSSSI had clinical resolved, per local practice. There were an additional two cases in the comparator arm where the investigator increased the dosing frequency during the course of therapy which was not taken into account or captured since only one planned dose frequency could be captured for a given route. This resulted in an underestimation of the planned number of doses.*

Prior and Concomitant Medications

A slightly larger proportion of treated patients in the tedizolid arm received prior short-acting antibacterial therapy for the primary ABSSSI before randomization, 29% for tedizolid versus 21% for the comparator. The most commonly reported prior antibacterial treatment was amoxicillin-clavulanate. There were no prohibited concomitant antibacterials used. Two patients (one in each arm) used concomitant metronidazole which was allowed under the protocol in patients with wound infections when Gram-negative pathogens were suspected or confirmed. One patient in the tedizolid arm received paroxetine (a SSRI) before, during and after treatment which was not allowed under Amendment 5, however this patient was enrolled under a previous amendment.

Reviewer Comments: *The Applicant's defined rules for prior and concomitant therapy use were consistent with the Guidance and appeared to be appropriately followed. Since the prior antibacterial use was not used for more than 24 hours and was short-acting, it was not expected to meaningfully influence the primary endpoint at the TOC visit (18-25 days after the first dose). However, subgroup analyses by prior antibacterial therapy were conducted to further explore this issue.*

Timing of I&D Procedure

Given the unblinded study design, the randomized treatment could have influenced the investigators' decisions to perform I&D. The following describes when the I&D procedure occurred in relation to randomization and initiation of study treatment (as reported in a January 22, 2020 submission by the Applicant).

- Overall, 22 (18%) of patients had I&D captured as a procedure, 16 (18%) in the tedizolid arm and 6 (21%) in the comparator arm.
- The majority of patients had I&D prior to Day 1 or on Day 1 prior to randomization, four patients (2 in the tedizolid arm and 2 in the comparator arm) may have had I&D on Day 1 after randomization.
- Two patients (1 in each arm) had I&D after randomization. In 1 case (tedizolid arm) it was performed the day after randomization and in the other case (comparator arm) it was performed on Day 28 for a new abscess in a new location.
- The physician making the determination to perform an I&D was not necessarily blinded.

***Reviewer Comments**: At most, there were six cases where investigators could have had knowledge of treatment assignment prior to performing I&D, 3 (3%) in the tedizolid arm and 3 (10%) in the comparator arm. All six of these patients were clinical successes at TOC. In one case (tedizolid arm) the I&D was performed on Day 28 subsequent to the TOC evaluation. Due to the small numbers of cases and the lack of major imbalances favoring the tedizolid arm (the imbalances actually favored the comparator arm), the decision to perform I&D likely did not result in substantial study biases.*

Rescue Medication Use

There was one patient (b) (6) in the tedizolid arm who took effective concomitant therapy prior to EOT who was assessed as a clinical failure in the primary analysis. There were no other patients who received rescue therapy in either study arm. Note that there was only one other clinical failure in the study (patient (b) (6) in the comparator arm).

Efficacy Results – Primary endpoint

Table 18 shows results for the primary efficacy endpoint which was defined as the clinical success rate at the TOC visit and the primary analyses evaluated it in the ITT and CE-TOC analysis populations respectively. In the ITT analysis set, success rates were 88/91 (96.7%) in the tedizolid arm versus 27/29 (93.1%) in the comparator arm, with a treatment difference (tedizolid minus comparator) of 3.6% (95% CI: -6.3%, 13.5%). In the CE-TOC population, success rates were 87/87 (100%) versus 26/27 (96.3%), with a difference of 3.7% (95% CI: -3.4%, 10.8%). Note that this analysis was descriptive and was not intended for drawing statistical inferences.

In the ITT analysis set, there were two patients (one in each arm) assessed as a clinical failure at the TOC visit and three patients (two in the tedizolid arm, one in the comparator arm) assessed as indeterminate at TOC. As shown in **Table 19**, the three patients with indeterminate

outcomes withdrew from the study only one day after receiving study drug (on Day 2) for various reasons. The extent to which these withdrawals were related to the study drug received is not clear. However, since the patients with missing/indeterminate data were relatively small in number and balanced between the treatment arms, the impact of missing data was minimal. Sensitivity analyses which considered indeterminates as successes rather than failures showed findings that were consistent with the primary analysis.

Table 18: Efficacy Results – Primary Endpoint

Clinical Response at TOC Visit	Tedizolid (N=91)	Comparator (N=29)	Diff (95% CI)
ITT Analysis Set			
Success	88 (96.7%)	27 (93.1%)	3.6 (-6.3, 13.5)
Clinical Failure	1 (1.1%)	1 (3.4%)	
Indeterminate	2 (2.2%)	1 (3.4%)	
CE-TOC Analysis Set			
Success	87/87 (100%)	26/27 (96.3%)	3.7 (-3.4, 10.8)
Clinical Failure	0	1 (3.7%)	

Source: Partially Adapted from Applicant Table 11-1 in CSR

Table 19: Description of Clinical Failures/Indeterminates at TOC

Patient ID	Treatment Arm	Description
Clinical Failures		
(b) (6)	Tedizolid	Discontinued treatment and withdrew from study due to AE on Day 2. Received effective concomitant therapy prior to EOT.
	Comparator	Completed study receiving 10 days of therapy. Assessed as clinical failure at EOT and at TOC
Indeterminates		
	Tedizolid	Patient withdrew from study on Day 2
	Tedizolid	Patient discontinued and withdrew from study due to gram-negative infection on Day 2
	Comparator	Withdrew by investigator at Day 2 due to pathogen resistant to available oral antibiotics

Source: Reviewer Table

Data Quality and Integrity

The statistical and clinical review teams evaluated the data and analysis quality with assistance from the Office of Computational Science (OCS). This included an assessment of the compatibility of the data with the review tools and data quality metrics such as the availability of appropriate variables, variables populated by expected data points and the appropriate use of standard terminology. In general, the data submitted by the Applicant were acceptable.

Efficacy Results – Secondary and other relevant endpoints

Efficacy results for the key secondary endpoints, the responder rate at 48-72 hours and the clinical success rate at the EOT visit, are shown below for the ITT analysis set. As in the primary analysis, responder/success rates were high in both treatment arms. At the 48-72 hour visit, responder rates were 84/91 (92.3%) in the tedizolid arm versus 28/29 (96.6%) in the comparator arm, a difference of 4.2% (-12.9%, 4.4%). At the EOT visit, clinical success rates were 88/89 (96.7%) versus 28/29 (96.6%), a difference of 0.2% (95% CI: -7.4%, 7.7%). Identical findings were observed for comparisons of sustained clinical success rates at the LFU visit. Of the four patients who were not categorized as a sustained clinical success at the LFU visit, only one patient in the tedizolid arm was assessed with a clinical relapse at the LFU visit.

Table 20: Clinical Success/Responders by Study Visit (ITT)

Clinical Response	Tedizolid (N=91)	Comparator (N=29)	Diff (95% CI)
At 48-72 hrs (key secondary endpoint)			
Responder	84 (92.3%)	28 (96.6%)	-4.2 (-12.9, 4.4)
Failure	4 (4.4%)	0	
Indeterminate	3 (3.3%)	1 (3.4%)	
At EOT Visit (key secondary endpoint)			
Success	88 (96.7%)	28 (96.6%)	0.2 (-7.4, 7.7)
Clinical Failure	1 (1.1%)	0	
Indeterminate	2 (2.2%)	1 (3.4%)	
At LFU Visit (other endpoint)			
Success[1]	88 (96.7%)	28 (96.4%)	0.2 (-7.4,7.7)
Relapse	1 (1.1%)	0	
Indeterminate	2 (2.2%)	1 (3.4%)	

Source: Reviewer Table

1- 'Success' includes all sustained clinical successes (clinical successes at both TOC and LFU) as well as Patients (b) (6) (tedizolid) and (b) (6) (Comparator) who were clinical failures at TOC and clinical successes at LFU.

Reviewer Comments: *Although this study was not intended for drawing statistical inferences nor powered for showing non-inferiority, an examination of the difference in responder rates at 48-72 hours (the primary endpoint recommended by the Guidance for ABSSSI trials) would show a lower 95% confidence bound of -12.9%. This would be consistent with an assumption of non-inferiority based on M1 (a margin reflecting the entire known effect of the active control relative to placebo) but not for M2 (a margin reflecting the portion of the control effect that is important to preserve with the test drug, based on clinical judgement). According to the ABSSSI Guidance, M1 is estimated to be approximately 20% based on historical trials while an appropriate NI margin of interest is generally set to equal M2 (i.e. 10%).*

Favorable microbiological response rates (eradication or presumed eradication) at the TOC visit were similar in both treatment arms in the micro-ITT population, 45/48 (93.8%) in the tedizolid arm versus 16/16 (100%) in the comparator arm, as shown in **Table 21**. Microbiological response rates at the TOC visit were driven mainly by responses to *S. aureus* (specifically, MSSA). Comparisons of response rates for other bacterial species were limited due to small numbers.

Table 21: Favorable Microbiological Response Rates at TOC (Micro-ITT)

Response	**Tedizolid** N=48	**Comparator** N=16
Overall Microbiological Response		
Favorable	45 (93.8%)	16 (100%)
Unfavorable	2 (4.2%)	0
Indeterminate	1 (2.1%)	0
Per-patient Microbiological Response by Major Pathogen		
Staphylococcus aureus	N=42	N=14
Favorable	39 (95.1%)	14 (100%)
Unfavorable	2 (4.8%)	0
Indeterminate	1 (2.4%)	0
MRSA	N=2	N=1
Favorable	2 (100%)	1 (100%)
MSSA	N=36	N=12
Favorable	33 (91.7%)	12 (100%)
Unfavorable	2 (5.6%)	0
Indeterminate	1 (2.8%)	0
Streptococcus pyogenes	N=9	N=2
Favorable	8 (88.9%)	2 (100%)
Unfavorable	1 (11.1%)	0

Source: Reviewer Table

Durability of Response

The treatment difference for clinical success/responder rates was favorable across all time points which was consistent with a durable response. No patients in the micro-ITT population were diagnosed with a superinfection or a new infection at the TOC Visit. Overall, the sustained clinical success rates at the LFU visit among ITT patients were 96.7% in the tedizolid arm and 96.4% in the comparator arm. Only one patient (tedizolid arm) was categorized as a clinical success at TOC with a clinical relapse at the LFU visit. Since the LFU assessment could be conducted via telephone as well as in person depending on the patient's described symptoms, missing data rates were low, 2.2% in the tedizolid arm and 3.4% in the comparator arm.

Persistence of Effect

Persistence of effect was observed by comparing treatments according to the changes in signs and symptoms of the primary ABSSSI including the lesion size. Measurements of these signs and symptoms were not performed daily, however, the percentage of patients with complete resolution of the lesion size (100% reduction) and all other signs and symptoms was compared across the following visits (e.g. 48-72 hours, at Day 7, at EOT and TOC) to investigate persistence of effect. Comparisons appeared to be favorable among patients in the tedizolid arm across these visits, as shown in **Table 23**.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

There was an exploratory endpoint considered based on mean pain intensity ratings reported by patients, based on the Wong-Baker faces rating scale. The mean pain intensities reported at the Screening Visit in the tedizolid and comparator groups and at the EOT Visit were comparable.

Subgroup Analyses

Subgroup comparisons of overall success rates were performed by gender, race, geographic region, infection type and lesion area. There were no notable differences in these subgroups due to the high success rates in both treatment arms and the limited numbers of patients in each subgroup, especially in the comparator arm. Success rates in the tedizolid arm were slightly lower in patients with wound infections at baseline as well as patients with larger baseline lesions (lesions with a surface area of at least 150 cm^2).

Table 22: Subgroup Analyses of Clinical Response at TOC (ITT Population)

Clinical Success Rates at TOC by Subgroup	Tedizolid (N=91) n (%)	Comparator (N=29) n (%)	Diff (95% CI)
Sex			
Male	57/58 (98.3%)	16/17 (94.1%)	4.2 (-7.5, 15.8)
Female	31/33 (93.9%)	11/12 (91.7%)	2.3 (-15.4,19.9)
Age Group			
12-14 years	43/43 (100%)	13/14 (92.9%)	7.1 (-6.4, 20.6)
15-17 years	45/48 (93.8%)	14/15 (93.3%)	0.4 (-13.9, 14.8)
Race			
White	77/80 (96.3%)	23/24 (95.8%)	0.4 (-8.6, 9.4)
Not White	11/11 (100%)	4/5 (80.0%)	20.0 (-15.1, 55.1)
Geographic Region			
North America	7/8 (87.5%)	2/2 (100%)	-12.5 (-35.4, 10.4)
Europe	69/71 (97.2%)	22/23 (95.7%)	1.5 (-7.6, 10.7)
South Africa	12/12 (100%)	3/4 (75%)	25.0 (-17.4, 67.4)
Infection Type			
Cellulitis/erysipelas	38/38 (100%)	10/10 (100%)	0.0 (0.0, 0.0)
Major Abscess	39/40 (97.5%)	10/11 (90.9%)	6.6 (-11.1, 24.3)

Wound Infection	11/13 (84.6%)	7/8 (87.5%)	-2.9 (-33.0, 27.3)
Prior Antibiotic Therapy			
Yes	33/34 (97.1%)	5/6 (83.3%)	13.7 (-16.6, 44.1)
No	55/57 (96.5%)	22 995.7%)	0.8 (-8.8, 10.4)
Fever			
Yes	57/59 (96.6%)	15/15 (100%)	-3.4 (-8.0, 1.2)
No	31/32 (96.9%)	12/14 (85.7%)	11.2 (-8.1, 30.5)
Lesion Area			
< 75 cm^2	29/29 (100%)	13/14 (92.9%)	7.1 (-6.3, 20.6)
75 to <150 cm^2	42/43 (97.7%)	10/11 (90.9%)	6.8 (-10.8, 24.3)
≥ 150 cm^2	17/19 (89.4%)	4/4 (100%)	-10.5 (-32.0, 4.1)

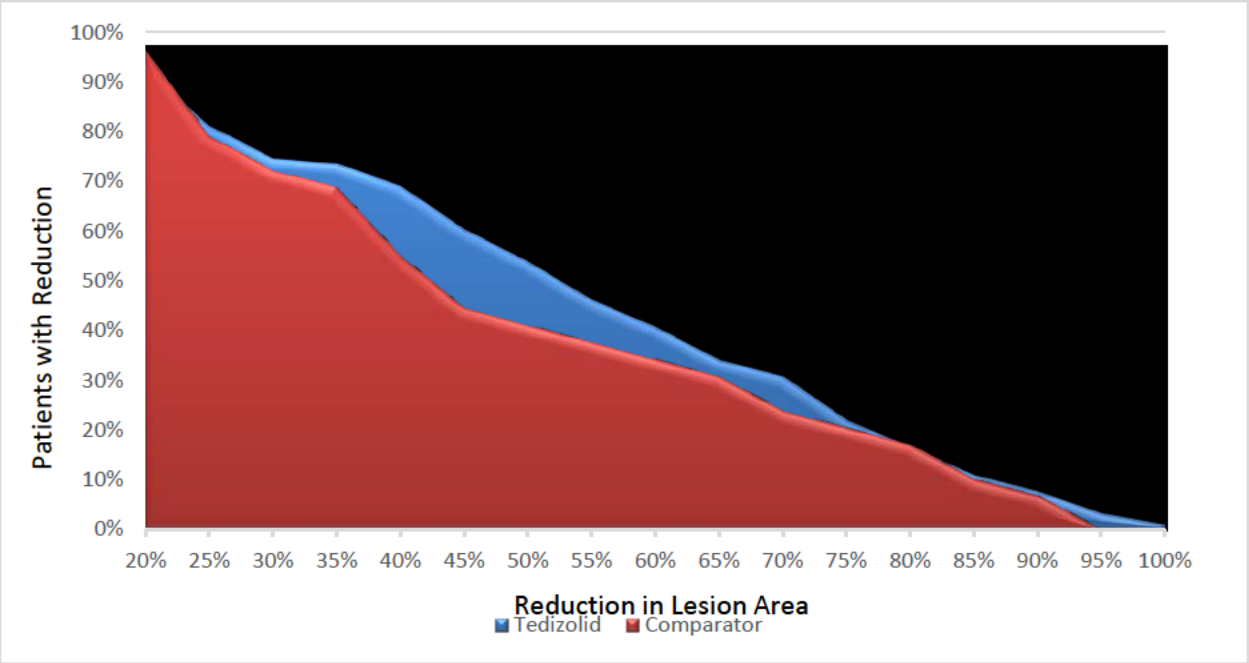
Source: Reviewer Table

Additional Analyses Conducted on the Individual Trial

Reductions in Lesion Area

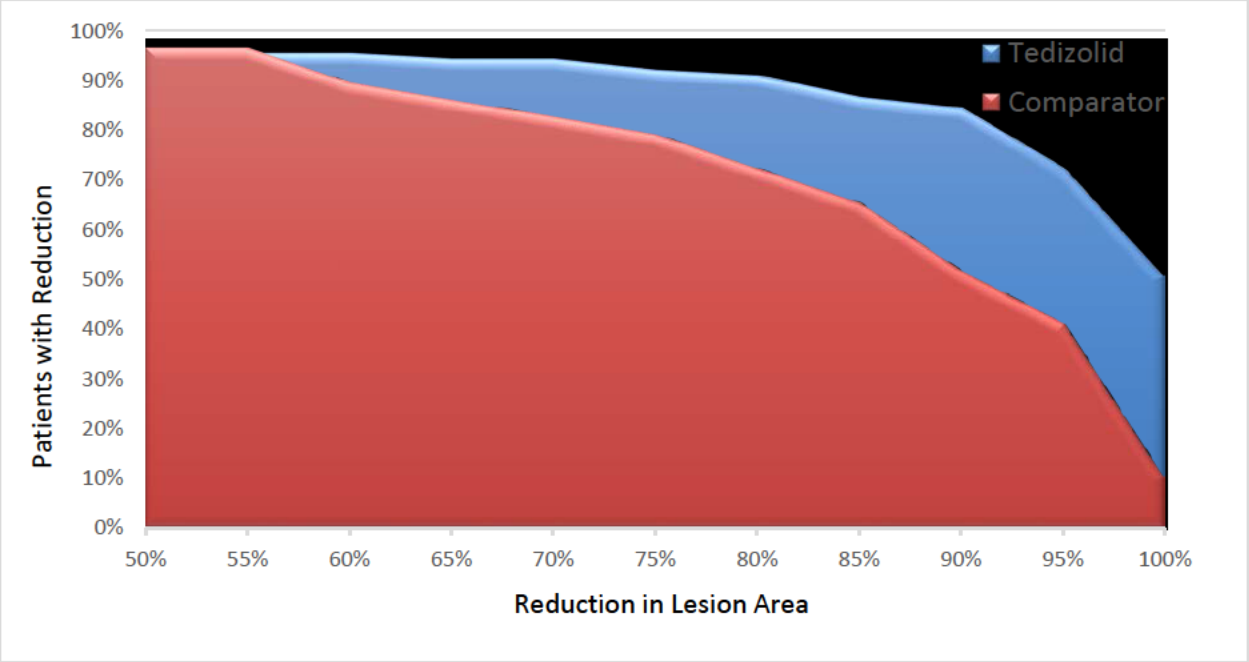
The Reviewer performed additional analyses which considered the distribution of reductions in lesion area at 48-72 hour and the Day 7 visits in **Figure 3** and **Figure 4** respectively. Even though a larger percentage of patients achieved a 20% reduction in lesion area at 48-72 hours in the comparator arm, there was generally a larger percentage of patients in the tedizolid arm achieving reductions at or above larger percentage cut-offs. This was clearest for percentage reductions of 40% and 60% at 48-72 hours. By Day 7, nearly all ITT patients achieved at least a 50% reduction in lesion area. In general, patients in the tedizolid arm had larger percentage reductions at Day 7, this was especially pronounced for percentage reductions from 90% to 100%.

Figure 3: Distribution of Reductions in Lesion Area at 48-72 hours (ITT Population)



Source: Reviewer Figure

Figure 4: Distribution of Reductions in Lesion Area at Day 7 (ITT Population)



Source: Reviewer Figure

Complete Resolution Rates across Study Visits

In **Table 23**, the Reviewer compared treatments with respect to the percentage of patients with complete resolution (100% reduction) of lesion size as well as complete resolution or absence of all other baseline signs and symptoms of the primary cSSSTI which included erythema, fluctuance, induration, localized warmth, pain/tenderness, tenderness on palpation, drainage, and swelling. In both of these comparisons, differences in complete resolution rates were at least as favorable in the tedizolid arm with the largest differences observed at Day 7. At Day 7, 50.5% of tedizolid patients achieved complete resolution (100% reduction) of their baseline lesion versus 10.3% in the comparator arm and 51.7% achieved complete resolution or absence of other baseline signs and symptoms versus 17.2% in the comparator arm.

Table 23: Complete Resolution Rates of Lesion Area, Signs and Symptoms, and Regional or Systemic Signs (ITT Population)

Complete Resolution Rates	Tedizolid (N=91) n (%)	Comparator (N=29) n (%)	Diff (95% CI)
Baseline Lesion Area			
48-72 hour visit	1 (1.1%)	0 (0.0%)	1.1 (-10.3, 6.3)
Day 7 visit	46 (50.6%)	3 (10.3%)	40.2 (25.1, 55.3)
EOT	72 (79.1%)	19 (65.5%)	13.6 (-5.6, 32.8)
TOC	85 (93.4%)	26 (89.7%)	3.8 (-8.5, 16.0)
Baseline Signs and Symptoms of Primary cSSTI			
48-72 hour visit	1 (1.1%)	0 (0.0%)	1.1 (-10.3, 6.3)
Day 7 visit	47 (51.7%)	5 (17.2%)	34.4 (17.3, 51.6)
EOT	74 (81.3%)	23 (79.3%)	2.0 (-14.8, 18.8)
TOC	85 (93.4%)	27 (93.1%)	0.3 (-10.2, 10.8)

Source: Reviewer Table

Reviewer Comments: *The results at Day 7 should be viewed with caution as these are exploratory analyses with no control of the type I error rate. The timing of the Day 7 visit would also be expected to favor a therapy with a duration of 6 days versus a therapy of 10 days. Note that the number of patients with missing assessments (counted as not having complete resolution) was similar across study visits. At Day 7, there were 4 patients with missing assessments (3 patients in the tedizolid arm, 1 in the comparator arm).*

8.1.3. Assessment of Efficacy Across Trials

Study MK-1986-012 was the only study used to support efficacy and safety of tedizolid in the treatment of ABSSSI in an adolescent population. Two Phase 3 studies in adults for this indication have been previously reviewed. Treatment differences in clinical responder/success rates were similar between the two studies in adult patients which demonstrated noninferiority to the comparator (linezolid) and Study MK-1986-012. In the two adult studies, clinical success

rates were substantially lower than what was observed in adolescents which was likely due to a younger and patient population with less severe disease. In the adult studies, tedizolid showed clinical success rates based on a 20% reduction in lesion size at 48-72 hours of 78.0% and 85.2%, respectively, compared to 92.3% in the current trial. At the post-therapy evaluation (7-14 days after the end of therapy), clinical success rates in the tedizolid arm were 85.5% and 88.0%, compared to 96.7% in the current trial.

8.1.4. Integrated Assessment of Effectiveness

Study MK-1986-012 was the only study used to support efficacy and safety of tedizolid in an adolescent population with ABSSSI. This study showed a high rate of clinical success at the TOC visit which was similar in the tedizolid and comparator arms. These findings were robust to the choice of the analysis sets and time points. Findings in other efficacy endpoints were supportive of primary analysis findings. Microbiological success rates were high overall and similar between treatment arms. Results from this trial support the efficacy of tedizolid in the treatment of ABSSSI in adolescents.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety information from the adult studies will be summarized and the safety review will be based on a single-blind, 3:1 randomized, multicenter, active-controlled study (MK-1986-012). For the safety analysis, J Review 12.0 analytical software was utilized. The Applicant used MedDRA dictionary version 17.0.

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 *Clostridioides difficile*-associated diarrhea.

8.2.2. Review of the Safety Database

Overall Exposure

The Safety Analysis Set (the safety population) in MK-1986-012 included all 120 participants enrolled in the study, with 91 patients in the tedizolid arm and 29 patients in the comparator arm. Nearly 97% of ITT/Safety patients completed study treatment and completed the study as per protocol. The majority of participants of this study were male (63%), white (87%), and European (78%), with a mean age of 14.4 years (see Table 13 in Section 8.1.2).

The median duration of therapy was 6 days in the tedizolid group compared to 10 days for the comparator group. Nearly all patients started with IV therapy and switched to oral therapy. A smaller percentage of participants in the tedizolid group switched from IV to oral therapy (45% vs. 66%); however, those who switched in the tedizolid group generally switched earlier than

those in the comparator group (at 2-3 days vs. >/= 4 days; see Tables 15 and 16 in section 8.1.2). The most common initially used comparator drugs were cefazolin (11 participants; 4 of whom were switched to oral cephalexin or clindamycin), vancomycin (8 participants; 6 of whom were switched to oral cephalexin, clindamycin, or flucloxacillin), and linezolid (5 participants).

The safety population provided an adequate number of exposed patients at the proposed dose and duration of therapy, of 200 mg IV or PO once daily for 6 days. Due to the relatively small database overall, conclusions regarding safety in this pediatric population are limited.

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.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

In this pediatric study, the safety was evaluated with adverse events (AEs), physical examination, laboratory data, vital signs, and basic neurologic examination with cranial nerve assessments. Patients were followed for 30 days after receiving 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 (CRFs). All treatment emergent AEs (TEAEs) that, in the opinion of the Investigator, may have been infusion related were identified as such on the AE e-CRF.

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 Medical Dictionary for Regulatory Activities (MedDRA, v17.0) 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.

8.2.4. Safety Results

Table 24 displays the categorization of AEs. There were a total of 16 patients with AEs, 13 in the tedizolid group (14.3%) and 3 in the comparator group (10.3%).

Table 24: Categorization of adverse events

Adverse Event Category	Tedizolid phosphate n=91	Comparator n=29	Totals n=120
Any Adverse Event (AE)	13 (14.3%)	3 (10.3%)	16 (13.3%)
Any Treatment-Emergent AE (TEAE)	13 (14.3%)	3 (10.3%)	16 (13.3%)
Drug-Related TEAE	3 (3.3%)	1 (3.4%)	4 (3.3%)
TEAE Leading to Discontinuation of Study Drug	1 (1.1%)	0 (0.0%)	1 (0.8%)
TEAE Leading to Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious TEAE	1 (1.1%)	0 (0.0%)	1 (0.8%)
Drug-Related Serious TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious TEAE leading to Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious TEAE Leading to Discontinuation of Study Drug	1 (1.1%)	0 (0.0%)	1 (0.8%)

Source: Adapted from Table 12-1 from MK-1986-012 clinical study report and confirmed by reviewer

Deaths

No deaths due to any cause were reported in this study.

Serious Adverse Events

All TEAEs were mild to moderate except for the three serious and severe adverse events (pneumonia, sepsis, and venous thrombosis of the limb) which all occurred in the same patient in the tedizolid group as described below.

Subject (b) (6), a 16 year old white female with history of influenza (resolved), bronchitis (resolved), other unspecified acute respiratory viral infection (resolved), animal bite of right lower leg (reported resolved 2 years prior) and autonomic dysfunction (ongoing) was started on intravenous tedizolid on (b) (6) (or day 1 of study treatment) for a wound infection of the right foot. The patient was initially admitted to the General Unit on (b) (6) (day -1) for an "additional incision" as reported in patient's case report form and started on ampicillin (received two doses at 1700 and 2330 on (b) (6) (day -1)). On (b) (6) (day 1), she developed shortness of breath, right-sided chest pain, and right leg pain, and was found to have thrombocytopenia (platelet count 95 x 10^9/L), an apparent bilateral pneumonia confirmed by chest x-ray, and thrombosis of deep and superficial veins of the right leg (confirmed by

ultrasound), and was started on metronidazole (per narrative on day 1 only). On (b) (6) (day 2) she was transferred from the General Unit to the Intensive Care Unit after she began showing signs of sepsis and was started on ceftriaxone and oxacillin (for pneumonia and sepsis) and heparin (for thrombosis). The patient discontinued the study drug on day 2. Prior to starting the study drug, blood and deep wound cultures from (b) (6) (day 1) were found to be growing MSSA. AEs of pneumonia, sepsis and thrombosis (severe and serious) were not considered related to the study drug.

Comment: This reviewer agrees with the investigator that these three SAEs are unlikely to be drug-related. Given patient's positive MSSA blood and deep wound culture, this patient's presentation appears to be quite consistent with MSSA bacteremia and subsequent septic shock, DIC (disseminated intravascular coagulation), and ARDS (acute respiratory distress syndrome) secondary to the patient's MSSA ABSSSI (foot wound). The acuity of the development of this specific constellation of signs and symptoms in the setting of a positive wound and blood culture for MSSA are much more likely to be secondary to septic shock than they are to be related to tedizolid. It is possible that the ARDS was perceived as bilateral pneumonia on physical exam and chest x-ray and likely that the thrombocytopenia and venous thrombosis are secondary to DIC. The patient's acute respiratory and hematologic decompensation may have been complicated by her history of recurrent respiratory tract infections and autonomic dysfunction. It is also possible she developed pneumonia (vs. ARDS) from her disseminated S. aureus.

Dropouts and/or Discontinuations Due to Adverse Effects

There were four participants who discontinued both the study treatment and the trial itself: 3 in the tedizolid group and 1 in the comparator group.

The three discontinuations in the tedizolid arm were due to the AEs noted above (Subject (b) (6) a patient withdrawal, and a gram-negative infection. The patient withdrawal occurred on day 2 after the patient received 2 doses of study drug. No other explanation was provided. The discontinuation in the comparator arm was due to other reasons (i.e., patient met criteria for oral switch but the isolated pathogen was resistant to the available oral antibacterial drugs). See Table 19.

Significant Adverse Events

No other significant adverse events were reported.

Treatment Emergent Adverse Events and Adverse Reactions

There were 13 patients (14.3%) with TEAEs in the tedizolid arm vs. 3 (10.3%) in the comparator arm. TEAEs (occurring in greater than or equal to 2% of patients) thought to be possibly drug-related include elevated CPK (2, 2.2%), phlebitis (3, 3.3%), and elevated hepatic enzymes (3, 3.3%) in the tedizolid group and nausea (1, 3.4%) in the comparator group.

Table 25 below presents the TEAEs reported in the trial. Most AEs were mild in severity. There were 3 SAEs reported that all occurred in one patient in the tedizolid group: see narrative above. No SAEs occurred in the comparator arm.

Table 25: Adverse events (irrespective of causality) in the MK-1986-012 trial

Dictionary Derived Term	Tedizolid phosphate N=91	Comparator N=29
Phlebitis	3 (3.3%)	0 (0.0%)
Blood creatine phosphokinase increased	2 (2.2%)	0 (0.0%)
Liver function test abnormal	3 (3.3%)	0 (0.0%)
Nausea	0 (0.0%)	1 (3.4%)
Respiratory tract infection	0 (0.0%)	1 (3.4%)
Abscess limb	1 (1.1%)	0 (0.0%)
Asthenia	1 (1.1%)	0 (0.0%)
Headache	0 (0.0%)	1 (3.4%)
Anaemia	1 (1.1%)	0 (0.0%)
Pneumonia	1 (1.1%)	0 (0.0%)
Respiratory tract infection viral	1 (1.1%)	0 (0.0%)
Sepsis	1 (1.1%)	0 (0.0%)
Venous thrombosis limb	1 (1.1%)	0 (0.0%)
Viral pharyngitis	1 (1.1%)	0 (0.0%)
Vomiting	1 (1.1%)	0 (0.0%)
Total	13 (14.3%)	3 (10.3%)

Source: J review generated data

Comment: The Applicant, in their safety datasets, reported elevated transaminases in the tedizolid arm (3.3%) and nausea (3.4%) in the comparator to be causally related to the study drug. However, phlebitis (3.3%) can be associated with intravenous infusion, and here, is noted to be at a higher frequency than in the comparator arm. Infusion-related adverse reactions from the adult ABSSSI trials are also listed in Section 6.1 of the label. Therefore, phlebitis is included in the table of adverse reactions.

Two patients with elevated CPK are noted in the table above, and 3 additional cases were found who had elevated CPK around day 6 of therapy. An information request was sent to the Applicant on January 10, 2020, to provide case narratives including seriousness, causality, resolution, medical history, concomitant medications, other laboratory abnormalities for the following patients: (b) (6) The Applicant submitted the response to this IR on February 6, 2020.

Comment: The CPK elevations seem unrelated to the study drug in terms of temporal association. Most of the cases had mild elevation, other than a case who had started weightlifting and a case who had a CPK of 895 U/L at a remote time point. These patients were asymptomatic and did not appear to have had rhabdomyolysis or cardiac injury. It is unusual that four of these cases presented from one site. Laboratory error is certainly a possibility.

There were three patients noted to have elevated hepatic enzymes in the tedizolid arm (2 patients with increased ALT and 1 patient with increased AST) all of which were <3x ULN; one of which was thought to be possibly drug-related due to associated eosinophilia, however, therapy was not modified. The ALT levels declined to normal by the LFU visit.

Laboratory Findings

Liver Tests

Elevation of ALT, with a shift from within the normal range to above the upper limit of normal between screening and EOT was more commonly observed in the tedizolid group vs. the comparator group (12.9% vs. 4.8%, respectively); however, there were no notable differences between groups in mean and median changes of ALT. Also, 23.3% of the tedizolid group vs. 13% of the comparator group had at least a 1-grade shift (using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events) from baseline to the highest post-baseline value. Most of these elevations were mild and resolved before the LFU visit. Those that did not resolve were first observed near the end of the study or had been elevated at baseline and varied between Grade 0 and Grade 1 elevation. Four patients in tedizolid group were found to have 2- or 3-grade shifts from baseline. All, however, were receiving concomitant medications (e.g., acetaminophen or sevoflurane) for which elevated transaminases have been frequently reported. No patients discontinued study drug or the study because of these findings. None of the abnormal values were associated with elevated total bilirubin or other indicators of drug-induced liver injury.

Hematology

There were two patients noted to have anemia (with a hemoglobin <9 g (F) and hemoglobin <10 g (M)) and one patient noted to have thrombocytopenia (with platelets $<112x10^3/mm^3$) in the tedizolid arm. Each of these patients, however, had baseline anemia and thrombocytopenia respectively with minimal shift from baseline thereafter. More specifically, baseline values for each hematology parameter and the mean change from baseline at early clinical evaluation (ECE), EOT, and TOC were similar. Additionally, there were no patients who had a low absolute neutrophil count ($< 800/mm^3$) in either arm in the trial.

Vital Signs

Vital signs, including temperature, pulse rate, systolic blood pressure, and diastolic blood

pressure were monitored during the study. There were no potentially clinically significant changes.

Electrocardiograms (ECGs)

There were no significant ECG changes from baseline or evidence of QT prolongation in this study.

Neurological Assessment and Snellen Visual Acuity Score

The Applicant reported that there were no safety signals detected during neurological assessments or changes in visual acuity from baseline. The findings were comparable in both tedizolid and comparator.

Analysis of Submission-Specific Safety Issues

A safety assessment was also made comparing injection versus tablets to see if there were any specific safety findings associated with the formulations between the tedizolid and the comparator groups. Of note, vomiting, asthenia and phlebitis were all noted with tedizolid injection. The patient with pneumonia and venous thrombosis of the limb had AEs unrelated to the study drug (described in section 8.2.3).

No TEAEs involving serotonin syndrome, myelosuppression, lactic acidosis, peripheral neuropathy, optic neuropthy, specific drug-interactions, or *C. difficile*-associated diarrhea were identified.

8.2.5. Safety Analyses by Demographic Subgroups

This study enrolled patients who were predominantly male (63%), white (87%), and European (78%) with a mean age of 14.4 years (see Table 13 in Section 8.1.2).

Keeping in mind the limited sample size, there were no notable differences in safety signals among patients >18 years versus those aged 12 to <18 years and no differences noted in frequency of AEs among the demographic subgroups.

8.2.6. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Pregnant patients were excluded from the trial. Pregnancy was not reported as an adverse outcome.

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

Not applicable.

8.2.7. 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 of labeling has been updated to include information about infusion-related adverse reactions associated with IV tedizolid. Phlebitis was reported in three patients who received IV tedizolid in Study MK-1986-012.

Expectations on Safety in the Postmarket Setting

Tedizolid has undergone postmarketing surveillance since its approval. The Applicant reports that it closely monitors for the identified risk of myelosuppression and potential risks of serotonin syndrome, peripheral neuropathy, optic neuropathy, lactic acidosis, and emergence of drug resistance.

8.2.8. Integrated Assessment of Safety

Ninety-one pediatric patients aged 12 to less than 18 years of age with ABSSSI were exposed to tedizolid in a randomized, single-blind, multicenter, active-control study. The most common adverse reactions in adolescent patients were phlebitis (noted with only the intravenous formulation) (3%), increased hepatic transaminases (3%) and vomiting (1%). The rate of phlebitis (3%) in this trial was consistent with the rate of 4% infusion related reactions noted with tedizolid in the adult trials. The safety profile of tedizolid as studied in this pediatric trial was somewhat different to that noted in the adult population, in terms of lack of diarrhea or headache, but the number of patients was small and was a less sick population. There were no deaths and no significant safety concerns identified. There were no cases of lactic acidosis, hypoglycemia, optic neuritis, or *C. difficile*-associated diarrhea, as noted with other members of the class of the oxazolidinones. Overall, the safety profile for tedizolid in pediatric patients appears comparable to that of the adult population.

8.3. Statistical Issues

Efficacy findings from Study MK-1986-012 supported the efficacy of tedizolid in adolescent patients with ABSSSI under a broad range of assumptions. Note that this is a descriptive study with no planned hypothesis testing that was not intended for making statistical inferences. Although the design was limited due to it being unblinded, having a small sample size and not using a standardized comparator regimen, there were no major statistical issues identified.

The following issues identified were considered to be minor:

- There were cases in which unblinded investigators could make a decision regarding performing I&D in study patients. These cases were uncommon and balanced between study arms and likely would not meaningfully influence key study outcomes.
- Treatment compliance as reported in the study report was much lower in the comparator arm than in the tedizolid arm. This was likely due to limitations with standardizing the comparator treatment. Investigators who were unblinded could change the dosing frequency during the course of therapy. It is not clear how this lack of standardization may have affected treatment comparisons.
- Approximately 33% of patients in this study had lesion sizes at baseline that were less than 75cm^2. Such patients would not be included in ABSSSI studies following the guidance. A minimum lesion area of 75cm^2 at baseline better ensures adequate disease severity, reduces measurement error and is more consistent with populations used in defining the NI margin. Note, however, that this study was not intended for making inferences regarding noninferiority.
- The study was stopped prior to reaching its planned sample size for reasons which are unclear. We cannot rule out the possibility that the study was stopped based on knowledge of a favorable treatment effect during the trial which can result in biases.

8.4. Conclusions and Recommendations

The Applicant has provided adequate evidence of effectiveness to expand the ABSSSI indication to the new population of 12 years to less than 18 years of age as noted from the pharmacokinetic data and extrapolation of efficacy from adults. Clinical success rates were 96.7% in the tedizolid arm versus 93.1% in the comparator arm (treatment difference of 3.6%) at the TOC visit. The overall safety profile was comparable.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for these applications as external expertise was not considered necessary.

10 Pediatrics

Tedizolid was approved for ABSSSI in adults on June 20, 2014. The iPSP was submitted in 2013. Protocol amendments and deferral extension requests were made due to enrollment issues, and a deferral extension was granted on January 28, 2018. This study fulfills PREA PMR 2159-1. The pediatric assessment was discussed with the Pediatric Review Committee on March 17, 2020.

On January 15, 2020, the Division notified the Applicant that PREA PMR 2159-4, which was to "Conduct a Phase 1 Single-Dose Safety and Pharmacokinetic Study of Oral and IV SIVEXTRO (tedizolid phosphate) in Patients 2 years to <12 years of age" was fulfilled.

The following are the open pediatric PMRs:

- PMR 2159-5: Conduct a Phase 1 Single-Dose Safety and Pharmacokinetic Study of Oral and Intravenous SIVEXTRO (tedizolid phosphate) in Patients Under 2 Years Old. Deferral extension was granted on 01/29/18. Projected study completion date is 10/20. Final report submission date is 05/21.
- 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 of Acute Bacterial Skin and Skin Structure Infections in Pediatric Patients Aged Birth to <12 Years" is ongoing and the projected study completion date is 02/21. Final report submission date is 08/21.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Pertinent labeling changes which were agreed to with the Applicant included:

Revision of the pediatric subsection section 12 (Clinical Pharmacology) to state that although increased exposures were seen in adolescents, they were not clinically significant.

Revision to the clinical studies pediatric section to include clinical success rates and noting that the study was not powered for inferential statistics.

Similar terms like elevated AST, ALT, abnormal LFTs were combined in the adverse reaction section.

12 Risk Evaluation and Mitigation Strategies (REMS)

None.

13 Postmarketing Requirements and Commitment

No safety PMR/PMCs are required. Refer to section 10 for other PREA PMR studies.

14 Division Director (Clinical) Comments

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

15 Appendices

15.1. Financial Disclosure

The list of investigators and their curriculum vitae was provided and reviewed.
Covered Clinical Study (Name and/or Number): MK-1986-012

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 86, 1 investigator left site 420 but had no financial interests		
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)): None 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 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): 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

15.2. OCP Appendices

Population PK Analysis of Tedizolid in Adolescent ABSSSI Subjects

The applicant previously developed a population PK (PPK) model for tedizolid as a part of the original marketing application of SIVEXTRO based on PK samples collected in patients ages ≥17 years enrolled in 4 Phase 1 and 3 Phase 2/3 studies. This original PPK model had been reviewed by the Division of Pharmacometrics, and it was deemed to be acceptable for characterizing tedizolid PK in adult ABSSSI patients. To support extending the indication to adolescents and characterizing the PK of tedizolid in the adolescent population, the applicant re-estimated model parameters with the updated dataset including the pediatric/adolescent data in Study P013 (TR701-120/MK-1986-013; 2 to 12 years old) and Study P012 (TR701-122/MK-1986-012; 12 to 18 years old).

The PK dataset included data from 1312 subjects; adult ABSSSI subjects (n=945), adolescent ABSSSI subjects (n=103), and healthy volunteers (n=223), and hospitalized subjects (n=41). A total of 132 subjects were from the pediatric studies (Studies P012, P013, and P026), 91 of which were adolescent ABSSSI subjects and 41 were hospitalized subjects (including 20 adolescent subjects). The majority of the subjects were Caucasian (70.9% overall and 87.9% in Study P012) and male (67.4% overall, 63.7% in Study P012). The overall mean subject age was 40.7 years and ranged from 3 to 94 years. The mean (range) age in Study P012 was 15 (12 - 18) years old. The mean body weight (SD) was 77.6 (21.2) kg for all PK dataset versus 59.7 (17.3) kg for Study P012. (source: Table 14 and 15, pg. 70, M&S report)

The structural model for the final PPK model was a two-compartment model with linear elimination and absorption with lag time and sequential zero-order release into a depot compartment, and then first-order absorption from the depot to the central compartment. The applicant made adjustments to the previously developed model by 1) changing the reference population to the healthy volunteers for the impact of disease status on CL and Vc, and 2) incorporating the impact of weight on Q (in addition to CL, Vc, and Vp) and applying the same values for the power effect of weight on Q as the one on CL. Body weight and the disease status were the covariate implemented in the model. Parameter estimates from the applicant's final model (run412s) are presented in **Table 24**.

Table 24. PPK model parameter estimates for the final model

Parameter	Final Model[A] (run412s)		
	Fixed Effect[B] (%RSE)	IIV %CV[B] (%RSE)	Shrinkage[C,D] (%)
Infusion time (h)	0.810 FIXED	8.26 FIXED	32.3
F1	0.857 (0.965)	–	–
Zero-order duration (h)	0.175 (28.3)	258 (7.39)	41.1
Ka (h^{-1})	1.47 (9.25)	77.0 (8.36)	59.2
Lag time (h)	0.226 (0.0376)	100 (5.47)	56.8
CL (L/h)	5.39 (6.98)	32.2 (2.87)	14.6
~Weight [power model]	0.408 (10.2)	–	–
~Infection (%) [linear model]	22.0 (39.3)	–	–
Vc (L)	58.5 (3.36)	25.2 (4.67)	31.9
~Weight [power model]	0.903 (3.53)	–	–
~Infection (%) [linear model]	9.87 (37.4)	–	–
~Diabetes (%) [linear model]	-14.3 (22.2)	–	–
Q (L/h)	1.43 (4.09)	–	–
~Weight [power model]	Same as for CL	–	–
Vp (L)	15.6 (2.41)	15.8 (8.54)	70.9
~Weight [power model]	0.678 (6.87)	–	–
Correlation CL-Vc (%)	–	62.1 (5.28)	–
Residual variability (RV)	–	–	11.7
RV for non-Phase 3 studies (%)	12.3 (1.36)	–	–
RV for Study 104 and Phase 3 studies (fold)[F]	4.92 (4.63)	–	–
RV for oral data (fold)[F]	2.01 (5.22)	–	–

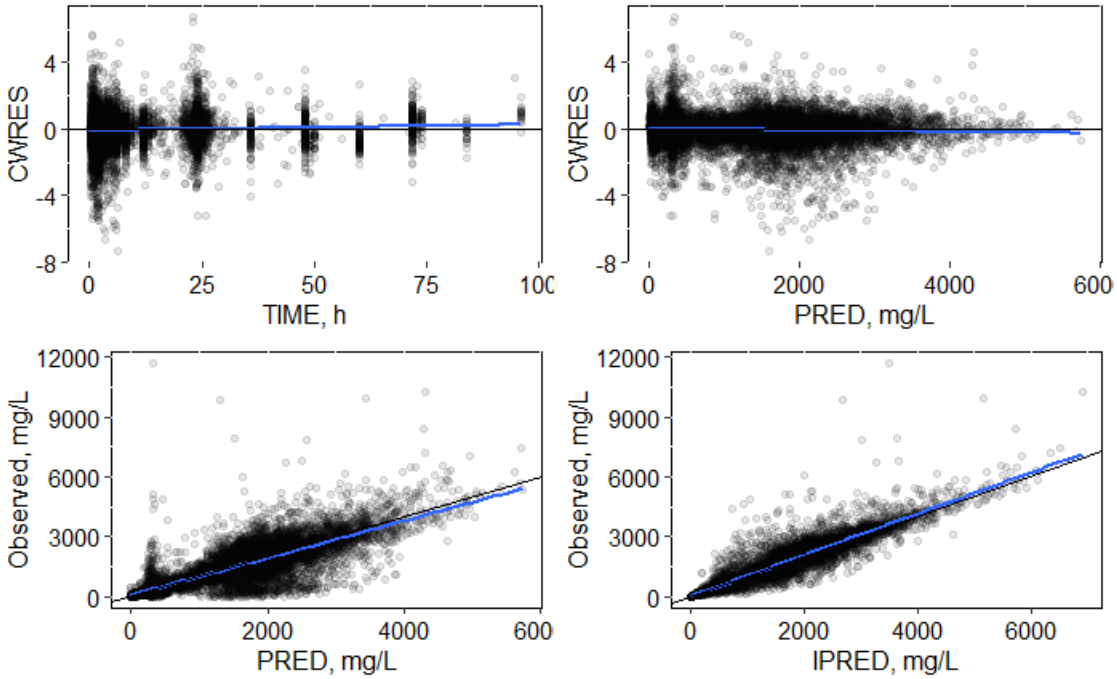
Source: Applicant's report (Table4, pg. 41, M&S report)

ABSSSI infection, diabetes, and total body weight were the only covariate effects present in the final PPK model. In the adolescent patients in Study P012, body weight was the influential covariate for tedizolid PK parameters (Tables 7 in M&S report) and the PPK analysis did not identify clear trends or specific impact of age or creatinine clearance on exposure (Table 8, and Figure 22 in M&S report).

Reviewer comment:
*The applicant's population PK model is acceptable for characterizing tedizolid PK in the pediatric population. Most parameters were estimated with acceptable precision (relative standard error < 10%), except for zero-order duration, and covariate effects (i.e., the infection on CL and Vc, and the diabetes on Vc) of which RSE > 20%. The shrinkage was high (> 40%) for most parameters and modest for CL (14.6%) and Vc (31.9%). The standard goodness of fit (GOF) plots (**Figure 5**) and GOF plots stratified by important covariates such as weight and age did not identify notable bias. The applicant's prediction corrected visual predictive check stratified by study demonstrated generally good agreement between the simulated and the observed profile*

(refer to Figure 33, pg. 94, M&S report). The reviewer found that the PK model reasonably described the observed data in the adolescent population.

Figure 5. Goodness of Fit plot for the final PPK model



Source: Generated by Reviewer using the applicant's final model

Tedizolid Exposure in Adolescent ABSSSI Subjects (Study P012)

The applicant estimated individual tedizolid plasma concentration-time profiles based on the individual Empirical Bayes Estimates (EBEs) and their actual treatment regimen. The applicant stated that the predicted exposures (AUC and Cmax after the first and last dose) in adolescent ABSSSI subjects from Study P012 were slightly higher than those in adult ABSSSI subjects from previous Phase 2 and 3 studies (**Table 25**). The applicant stated that because weight was identified as a covariate on tedizolid clearance and volume parameters, the difference in body weight distributions in the Study P012 and the adult population studies (Studies P007, P009, and P010) may contribute to the observed exposure differences. Though the exposure was slightly higher in adolescents, the distribution of exposures substantially overlapped between the adolescent and adult populations.

Table 25. PPK model Predicted Exposure After First and Last Dose in Adolescent (Study P012) and Adult ABSSSI Subjects (Previous Phase 2 and 3 Studies)

Population	Geometric mean [95% Confidence Interval]			
	$AUC_{0\text{-}24h\_day1}$ (µg·h/mL)	$AUC_{0\text{-}24h\_last}$ (µg·h/mL)	$Cmax_{\_day1}$ (µg/mL)	$Cmax_{\_last}$ (µg/mL)
Adult (N = 830)	22.4 [21.9, 22.9]	21.0 [20.4, 21.5]	1.81 [1.73, 1.90]	2.00 [1.94, 2.06]
Adolescent, Study P012 (N = 91)	26.6 [24.9, 28.4]	28.6 [26.6, 30.8]	2.61 [2.27, 3.01]	3.13 [2.89, 3.38]

Source: Applicant's report (Table 9, pg. 44, M&S report)

Reviewer Comments:

Since the shrinkage for most PK parameters were high, the reviewer further simulated the individual PK profiles for the subjects enrolled in the Study P012 using the post-hoc EBEs and generated individual time-concentration profiles overlaying with the observed concentrations. In general, the simulated profiles using EBEs was in good agreement with the observed data. Also, with the modest shrinkage for CL and Vc, the reviewer opines that estimated AUC values are reasonably reliable to be used in E-R analyses and PTA analyses and the influence of shrinkage is thought to be limited in these analyses.

The reviewer summarized PK parameters in the adolescent subjects enrolled in Study P012 by the route of administration (Table 26). Note that out of the 91 subjects enrolled in Study P012, five subjects (5.5%) received only oral doses, 47 (51.6%) subjects received only IV doses, and 39 (42.9%) switched from IV to oral doses. $AUC_{0\text{-}24h}$ were comparable among the different route of administrations (the oral, IV, and IV to oral) and Cmax, following IV only administration, is 1.6-fold higher than that following oral only administration.

Table 26. Summary Statistics for PK parameters in adolescent subjects (Study P012) by route of administration

		Geometric Mean [95% CI]	
Route of Administration	*N*	*$AUC_{0\text{-}24h}$ (ug*h/mL)*	*Cmax (ug*h/mL)*
200 mg IV to Oral switch	*39*	*28.1 [25.2 - 31.3]*	*2.70 [2.46 - 2.97]*
200 mg Oral[a]	*4*	*28.4 [22.0 - 36.8]*	*2.31 [1.81 - 2.93]*
200 mg IV[a]	*46*	*29.6 [26.4 - 33.2]*	*3.68 [3.29 - 4.12]*
All subjects[a]	*89*	*28.9 [26.8 - 31.1]*	*3.15 [2.91 - 3.40]*

Source: Reviewer's analysis based on the applicant's model-derived PK parameters.
[a]Two subjects who received only one dose were excluded in calculation of summary statistics for steady-state PK parameters

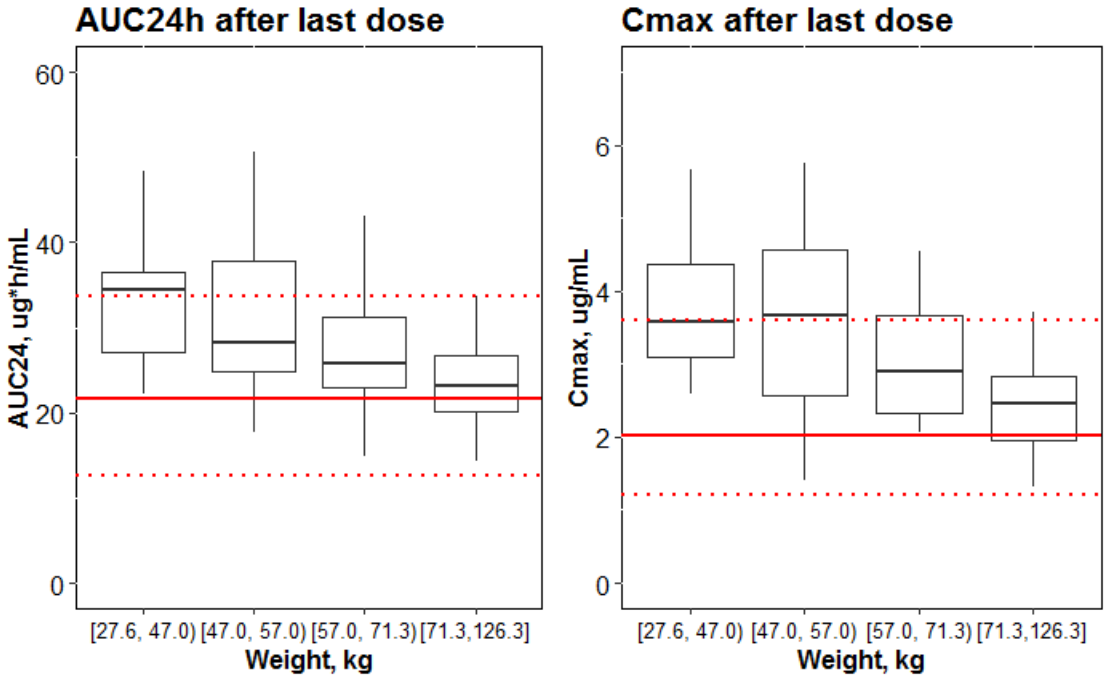
The reviewer's Table 27 *compares the estimated individual exposures between adolescent ABSSSI subjects from Study P012 and adult ABSSSI subjects from previous Phase 2 and 3 studies. The exposure in adolescent patients are 1.5- and 1.4-fold higher, for AUC and Cmax, respectively, compared to those in the adult patients. The proposed dose is the same (200 mg) for IV or oral administration, the summary PK parameters were calculated based on all subjects receiving oral only, IV only, or IV to Oral switch regardless of the route of administration. The result is consistent with the applicant's (Table 2).*

Table 27. Comparison of PK parameters between adolescent subjects (Study P012) and adults (Phase 2 and 3 studies)

Tedizolid exposure after the last dose (200 mg QD)	*Geometric Mean*		*GMR [90%CI]*
	[a]Adolescents	*[b]Adults*	
Cmax (ug/mL)	*3.15*	*2.04*	*1.54 [1.44-1.66]*
*$AUC_{0\text{-}24h}$ (ug*h/mL)*	*28.9*	*21.2*	*1.37 [1.28-1.45]*
Source: Reviewer's analysis based on the applicant's model-derived PK parameters. *[a]Adolescents (n=89) from the Phase 3 study (P012)* *[b]ABSSSI adult patients (n=817) from Phase 2 and 3 studies (104, 112,113, 16099, 16121).* *[a,b]Subjects who received < 2 doses were excluded in this analysis.*			

This observed high exposure (Table 27*) in adolescent were thought to be mainly due to the lower body weight in adolescent patients compared to adults. The mean body weight was 80.7 kg and 59.5 kg for the ABSSSI adult patients and the adolescent patients (Study P012) included in this analysis, respectively. Figure 2 presents comparison of tedizolid exposure in adolescent patients (Study P012) stratified by quartile weight groups.*

Figure 6. AUC and Cmax Stratified by Weight Quartiles



Red solid line represents median AUC and Cmax and the red dotted lines represent 5th and 95th percentiles of exposure for ABSSSI adults following 200 mg tedizolid administered by IV, oral, IV to oral switch.

Exposure-Response Analyses:
Exposure-Efficacy: The applicant explored the relationship between the individual AUC or fAUC/MIC and the primary efficacy endpoint, clinical response at TOC. Out of the 91 subjects in Study P012, 88 subjects (96.7%) achieved cure, 1 (1.1%) was a failure, and 2 (2.2%) had indeterminate clinical response. In graphical comparison of fAUC/MIC and $AUC_{0\text{-}24h\_last}$ between the subjects achieving cure and the one having failure, the applicant concluded that there were no clear trends observed between either fAUC/MIC or $AUC_{0\text{-}24h\_last}$ and the clinical outcome in Study P012 (Refer to Figure 14 and Figure 15, pg. 55, M&S Report).

Reviewer comment: *Due to the high response rate (n=88) out of 91 total subjects, inference on E-R relationship for efficacy is not feasible.*

Exposure-Safety: The applicant reported that TEAEs reported in 2 or more patients in the tedizolid group were blood creatine phosphokinase increased (n=2 [2.2%]) and phlebitis (n=3 participants [3.3%]). The applicant also conducted the exposure-safety analysis on "potentially clinically significant hematological events". The applicant reported that there were 5 hematological events reported in Study P012, all of which were due to decreased absolute neutrophil counts (Refer to Figure 19, pg. 55, M&S Report). The applicant concluded that there was no clear exposure-safety trend observed, noting that one subject had large $AUC_{0\text{-}24h}$ (145

μg*h/mL) and Cmax (11.3 μg/mL), versus mean AUC (28.9 μg*h/mL) and mean Cmax (3.15 μg/mL) observed in this study.

Reviewer comment: *Due to the low AE rate, E-R analysis for AEs was not performed by the reviewer. The applicant's analysis on hematological events is considered exploratory and the inference on relationship between the high exposure and the hematological is limited as this came from a single subject.*

Probability of Target Attainment Analysis in Adolescent ABSSSI Patients

The applicant simulated Tedizolid exposure for 1000 adolescent virtual subjects following 200 mg tedizolid phosphate once daily (QD) for 6 days administered under both IV and oral conditions independently. Then fAUC/MIC was calculated for each simulated subject over the range of MIC (0.015 to 16 ug/mL). The probability of PKPD target attainment (fAUC/MIC ≥3 determined in the animal infection models) was calculated. The applicant simulation predicted tedizolid to have 100 % PTA in adolescent patients up to MIC of 0.5 ug/mL (Table 10, pg. 46, M&S report).

Reviewer Comments: *The reviewer conducted independent PTA analysis using both Day 1 AUC_{0-24h} and Day 6 AUC_{0-24h} and was able to obtain the consistent conclusion as the applicant.*

% of Adolescent ABSSSI Subjects Achieving PK/PD Target										
MIC (μg/mL)	*0.015*	*0.03*	*0.06*	*0.12*	*0.25*	*0.5*	*1*	*2*	*4*	*8*
$fAUC_{Day\ 1}$/MIC=3										
IV	*100*	*100*	*100*	*100*	*100*	*100*	*94.5*	*30.5*	*0.3*	*0*
Oral	*100*	*99.9*	*99.9*	*99.7*	*99.3*	*98.3*	*80.9*	*9.4*	*0*	*0*
$fAUC_{Day\ 6}$/MIC=3										
IV	*100*	*100*	*100*	*100*	*100*	*100*	*97*	*46.5*	*2.1*	*0*
Oral	*100*	*100*	*100*	*100*	*99.9*	*99.9*	*91.2*	*28*	*0.3*	*0*
Source: Reviewer's analysis.										
% of Adolescent ABSSSI Subjects Achieving PK/PD Target (fAUC/MIC=3)										
MIC (μg/mL)	*0.015*	*0.03*	*0.06*	*0.12*	*0.25*	*0.5*	*1*	*2*	*4*	*8*
IV	*100*	*100*	*100*	*100*	*100*	*100*	*97*	*46.5*	*2.1*	*0*
Oral	*100*	*100*	*100*	*100*	*99.9*	*99.9*	*91.2*	*28*	*0.3*	*0*
Source: Reviewer's analysis.										

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/s/

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GURPREET K GILL SANGHA
06/17/2020 08:49:22 AM

CRISTINA M MIGLIS
06/17/2020 08:53:31 AM

KELLIE S REYNOLDS
06/17/2020 09:39:37 AM
Signing for Grace Yan Danielsen

JIHYE AHN
06/17/2020 09:41:35 AM

JUSTIN C EARP
06/17/2020 09:43:30 AM

MAYURIKA GHOSH
06/18/2020 08:40:24 AM

THOMAS D SMITH on behalf of AMY C BISHARA
06/18/2020 02:23:07 PM

THOMAS D SMITH
06/18/2020 02:24:23 PM

CHRISTOPHER E KADOORIE
06/18/2020 02:29:14 PM

KAREN M HIGGINS
06/18/2020 02:32:35 PM

SIMONE SHURLAND
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SIMONE SHURLAND
06/18/2020 02:37:25 PM

AVERY C GOODWIN
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ABIMBOLA O ADEBOWALE
06/18/2020 02:48:09 PM

CARMEN L DEBELLAS
06/18/2020 02:50:07 PM

SUMATHI NAMBIAR
06/18/2020 02:56:28 PM