30 January 2025
EMA/63803/2025
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Sivextro

International non-proprietary name: tedizolid phosphate

Procedure No. EMEA/H/C/002846/II/0054

Marketing authorisation holder (MAH): Merck Sharp & Dohme B.V.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation/Acronym	Definition
ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
ANC	absolute neutrophil count
AUC	area under the concentration-time curve
CDC	Centers for Disease Control and Prevention
CE-TOC	clinically evaluable at test of cure
CLSI	Clinical and Laboratory Standards Institute
C_{max}	maximum concentration
CoNS	coagulase-negative staphylococci
CSR	clinical study report
cSSSI	complicated skin and skin structure infections
cSSTI	complicated skin and soft tissue infections
DAIDS	Division of AIDS
DDI	drug-drug interaction
ECI	event of clinical interest
eGFR	estimated glomerular filtration rate
EOT	end of therapy
E-R	exposure-response
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GAS	group A streptococcus
GLP	Good Laboratory Practice
h	hour(s)
IBD	International Birth Date
IMW	ideal body weight
ITT	intention to treat
IV	intravenous(ly)
JAS	juvenile animal study(ies)
JMI	Jones Microbiology Institute
LFU	late follow-up
LLN	lower limit of normal
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MITT	microbiological ITT
MK-1986	tedizolid phosphate (SIVEXTRO™)
MRSA	methicillin-resistant *Staphylococcus aureus*

Abbreviation/Acronym	Definition
MSSA	methicillin-sensitive *Staphylococcus aureus*
NHANES	National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect level
PCS	potentially clinically significant
PD	Pharmacodynamic(s)
PFOS	powder for oral suspension
PIP	Pediatric Investigative Plan
PK	pharmacokinetic(s)
PND	postnatal day
PO	oral(ly)
PSP	Pediatric Study Plan
PT	preferred term
PTA	probability of target attainment
SAE	serious adverse event
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SSSI	skin and skin structure infections
SSTI	skin and soft tissue infections
STAR	SENTRY antimicrobial surveillance program
TK	toxicokinetics
T_{max}	time of maximum concentration
TMP/SMX	trimethoprim/sulfamethoxazole
TOC	test-of-cure
TR-700	Tedizolid: Biologically Active Moiety of Tedizolid Phosphate
TR-701 FA	Tedizolid Phosphate Free Acid Form
UK	United Kingdom
US	United States of America
vs	versus
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 2 July 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of paediatric patients aged from birth to less than 12 years for SIVEXTRO, based on final results from studies MK-1986-013, MK-1986-014 and MK-1986-018. MK-1986-013 is a single-dose trial to evaluate pharmacokinetics (PK) and safety of oral and intravenous (IV) administration of tedizolid phosphate in patients from 2 years to <12 years of age; MK-1986-014 is an open-label, multicentre, 2-part, single and multiple dose study to assess the PK of tedizolid phosphate and its active metabolite, tedizolid, and the safety of tedizolid phosphate following single and multiple dose IV and single oral dose. MK-1986-018 is a randomised, active controlled, investigator-blind, multicentre trial to evaluate safety and efficacy in patients from birth to less than 12 years of age; As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement minor editorial corrections.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions EMA/431901/2029, EMA/543132/2023 and EMA/90012/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0340/2023 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Fátima Ventura Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	2 July 2024
Start of procedure:	20 July 2024
CHMP Rapporteur Assessment Report	13 September 2024
PRAC Rapporteur Assessment Report	19 September 2024
PRAC members comments	25 September 2024
PRAC Outcome	3 October 2024
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 October 2024
Request for supplementary information (RSI)	17 October 2024
CHMP Rapporteur Assessment Report	6 January 2025
PRAC Rapporteur Assessment Report	7 January 2025
PRAC members comments	8 January 2025
Updated PRAC Rapporteur Assessment Report	9 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur Assessment Report	23 January 2025
Opinion	30 January 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Tedizolid phosphate (SIVEXTRO®, also known as MK-1986 or TR-701 FA) is an oxazolidinone-class antibacterial prodrug which is rapidly converted *in vivo* by phosphatases to the microbiologically active molecule, tedizolid (also known as TR-700). Tedizolid is primarily active against gram-positive pathogens and acts by inhibiting 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.

Tedizolid phosphate is currently approved in many countries and regions including the EU and US for the treatment of ABSSSI (also known as cSSTI or cSSSI) in adolescent patients (≥12 to <18 years of age)

and adults at a dosage of 200 mg administered once daily orally or as an IV infusion over 1 h for 6 days. In support of the marketing application for the treatment of ABSSSI in those patient age groups, evaluations of the nonclinical pharmacology, pharmacokinetics, and toxicology were completed.

The purpose of this variation application is to propose expanding the indications for IV use of tedizolid in patients from birth to <12 years of age (regardless of body weight) and for use of the oral tablet in paediatric patients weighing at least 35 kg. The dosing proposed for the pediatric population is based on attaining generally similar tedizolid exposures as in the adult population. A weight-banded dosing regimen is proposed for pediatric patients <35 kg body weight. The clinical data as well as additional toxicity data obtained from juvenile rats included in this supplemental marketing application support the safety and efficacy of IV use of tedizolid in patients from birth to <12 years of age (regardless of body weight) and for use of the oral tablet in patients <12 years of age and weighing at least 35 kg with ABSSSI.

Disease or condition

ABSSSI represents a subset of SSTI (also known as SSSI) comprising cellulitis, erysipelas, major cutaneous abscess, and wound infection. Staphylococcus aureus is the primary pathogen responsible for ABSSSI in paediatric and adult patients and accounts for at least 60% of ABSSSI cases globally, with substantial contributions from both MRSA and MSSA. Another important pathogen in ABSSSI in both paediatric and adult patients is the Group A beta-haemolytic streptococcus, Streptococcus pyogenes (ie, GAS). Other beta-haemolytic streptococcal species and anaerobic gram-positive organisms can also be responsible for ABSSSI, with considerable dependence on anatomical location of the site of infection.

State the claimed the therapeutic indication

The MAH initially proposed the following therapeutic indication for the tablet formulation (changes underlined):

Sivextro tablets are indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult patients and paediatric patients weighing at least 35 kg (see sections 4.4 and 5.1).

Additionally, the MAH initially proposed the following therapeutic indication for the IV formulation (changes underlined):

Sivextro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult and paediatric patients (see sections 4.4 and 5.1).

2.1.2. About the product

Tedizolid phosphate is an oxazolidinone-class antibacterial prodrug of the microbiologically active molecule, tedizolid, a protein synthesis inhibitor that has potent gram-positive bactericidal activity. The antibacterial activity of tedizolid is mediated by binding to the 50S subunit of the bacterial ribosome, resulting in inhibition of protein synthesis. Tedizolid phosphate is currently indicated for the treatment of ABSSSI (also known as cSSTI or cSSSI) in adults (≥ 18 years of age) and adolescents (12 to <18 years of age). Sivextro was approved in the EU on 23 March 2015.

2.1.3. The development programme

Development programme

The clinical development programme for Sivextro to support licensure in children < 12 years of age consists of three (two Phase 1 and one Phase 3) clinical studies.

The 2 Phase 1 studies, MK-1986-013 (P013) and MK-1986-014 (P014), evaluated the PK, safety, and tolerability of a single oral or IV dose of tedizolid phosphate in participants 2 to <12 years of age (P013) and from birth to <2 years of age (P014). P014 also included multiple-dose neonatal (full-term and preterm neonates from birth to <28 days of age) cohorts to evaluate the PK, safety, and tolerability of multiple IV doses of tedizolid phosphate in the neonatal age group.

The Phase 3 study, MK-1986-018 (P018), evaluated the safety and efficacy of multiple IV and oral doses of tedizolid phosphate in participants <12 years of age.

2.1.4. General comments on compliance with GLP

GLP studies were conducted in the USA, a member of OECD and therefore part of the OECD Mutual Acceptance of Data system. GLP compliance statements are included in the GLP study reports. The Juvenile Animal Studies (JAS) in rats were conducted at Charles River Laboratories Ashland, LLC, Ashland, Ohio, USA (formerly WIL Research, Ashland, Ohio, USA).

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

2.2.1. Introduction

In support of the original marketing application, comprehensive safety pharmacology and nonclinical toxicology evaluations were completed. Three JAS in rats were conducted after the approval of the original Marketing Application including an oral dose range finding study in juvenile Sprague Dawley rats, an oral juvenile animal study in Sprague Dawley to assess general toxicity, and an oral juvenile animal study in Long Evans rats to assess potential effects on development of the peripheral and central nervous system.

The metabolic profile of tedizolid phosphate has been fully characterized in rat, dog, and human; the similar profile supports that there are no unique metabolites in human, and the rat is an appropriate nonclinical species. In the general toxicity studies, the target organs of toxicity and NOAELs were similar in both the dog and rat following both IV and oral administration. Consistent with the ICH M3 (R2) and ICH S11 guidance, the JAS by the oral route were therefore conducted in the rat as the relevant species.

No additional fertility, embryo-fetal development or prenatal and postnatal development studies were conducted to support pediatric indications for tedizolid phosphate. JAS in rats were conducted with tedizolid phosphate and the results of these studies are discussed below.

As stated above, the main studies are GLP compliant.

Duration/ Study Type	Route	Species	Dose Levels (mg/kg/day)	NOAEL (mg/kg/day)	Study No. (GLP Status)
Reproductive & developmental toxicity (Studies in which the offspring, juvenile animals, are dosed and/or further evaluated					
Juvenile dose range finding toxicity and TK/14-days	Oral (gavage)	Juvenile Rat / Sprague Dawley	PND 7 to 20: 0, 3, 10, 30, 60	3	TE.701.TX.001 (Non-GLP)
Juvenile toxicity and TK/50-days with a 28-day recovery period	Oral (gavage)	Juvenile Rat / Sprague Dawley	PND 7 to 43: [a] 0, 1, 3, 10 D 43 to 56: 0, 2, 6, 20 (F); 0, 4, 12, 40 (M)	F: 3/6, M: 3/12 (general toxicity)	TE.701.TX.002 (GLP)
Juvenile toxicity and TK/50-days with a 90-day recovery period and special neurotoxicity assessments	Oral (gavage)	Juvenile Rat / Long Evans	PND 7 to 43: [a] 0, 1, 3, 10 PND 43 to 56: 0, 2, 6, 20 (F); 0, 4, 12, 40 (M)	F: 3/6, M: 3/12 (general toxicity) F: ≥10/20, M: ≥10/40 (neurotoxicity)[b]	TE.701.TX.003 (GLP)

F=female; GLP=Good Laboratory Practices; M=male; PND=postnatal day; No.=number; NOAEL = no-adverse-effect-level; TK=toxicokinetic.

[a] Doses levels were changed on PND 43 based on age- and gender-related differences in exposure.

[b] Study conducted to assess potential effects on development of the peripheral and central nervous systems.

2.2.2. Studies in which the Offspring (Juvenile Animals) are Dosed and/or Further Evaluated

2.2.2.1. Non-GLP Oral (Gavage) Dose Range-Finding Toxicity Study in Neonatal Sprague Dawley Rats (TE.701.TX.001)

The objectives of this study were to evaluate the potential effects of oral administration of tedizolid phosphate on neonatal growth and development in neonatal male and female rats as well as the TK profile of tedizolid phosphate and its active moiety, tedizolid, when administered for 14 consecutive days as a single daily dose from PND 7 through PND 20 for the purpose of selecting dose levels for a definitive JAS in Sprague Dawley rats.

Tedizolid phosphate, in the vehicle (25 mM disodium hydrogen phosphate buffered solution) was administered orally by gavage to 4 groups of 6 neonatal Sprague Dawley rats per sex, once daily for 14 consecutive days during PND 7 to 20. Doses were 3, 10, 30, and 60 mg/kg/day administered at a volume of 10 mL/kg. A concurrent control group composed of six males and six females received the vehicle on a comparable regimen.

Tedizolid phosphate was associated with dose-dependent body weight loss and/or lower body weight gains at 10, 30 and 60 mg/kg/day. Due to excessive toxicity and unscheduled deaths at 30 and 60 mg/kg/day, the surviving animals at these dose levels were terminated by PND 17. All rats in the 3 and 10 mg/kg/day groups survived to the scheduled necropsy on PND 21.

There were no changes in body weight gain at 3 mg/kg/day. At 10 mg/kg/day, there was a slight decrease in body weight gain.

Test article-related adverse changes in hematology parameters in the 10 mg/kg/day group, compared to concurrent controls included decreased mean red blood cell counts (-42% and -34%) and increased mean corpuscular volumes (+35% and +43%), mean corpuscular hemoglobin values (+29% and

+38%), hemoglobin distribution widths (+20% and +15%), and platelet counts (+34% and +32%) for males and females, respectively. In addition, decreased mean hemoglobin (-25%) and hematocrit (-22%) values and increases in mean absolute lymphocyte (+56%) and basophil counts were noted for males in the 10 mg/kg/day group compared to the control group. Similar trends were generally observed in the 30 and 60 mg/kg/day groups; however, interpretation was limited by the small sample size due to mortality. There were no adverse test article-related hematology effects observed at 3 mg/kg/day.

Test article-related adverse alterations in serum chemistry parameters in the 10 mg/kg/day group included higher mean bilirubin, as well as lower mean serum cholesterol (-15 % and -16%), globulin (-5% and -19%), and alkaline phosphatase (-19% and -33%) values for males and females, respectively, compared to the control group. In addition, an elevated albumin/globulin ratio (+27%) and triglyceride level (+132%) were noted for females in the 10 mg/kg/day group compared to the control group. There were no adverse test article-related serum chemistry effects observed at 3 mg/kg/day.

Test article-related, adverse histopathological effects were identified at non tolerated doses (30 and 60 mg/kg/day) in the kidney (mild to moderate cortical tubular dilation with granular debris), small intestine (mild to severe villous blunting), rectum (moderate mucosal mineralization), spleen (moderate to severe lymphoid hypocellularity), thymus (moderate to severe lymphoid hypocellularity), bone marrow (moderate to severe marrow hypocellularity), and heart (mild myofiber attenuation, Anitschkow and multinucleated cells). The bone marrow hypocellularity at these dose levels correlated with decreases in mean total white blood cell counts, red blood cell counts, platelet counts, and percent reticulocytes. There were no adverse histopathological changes at ≤10 mg/kg/day.

Exposure to tedizolid, in terms of $AUC_{0\text{-}24h}$ and C_{max}, was similar between both genders at all dose levels on PND 7. On PND 20, tedizolid exposure was similar between genders in the 3 and 10 mg/kg dose groups and was approximately 1.6- and 1.2-fold higher in females as compared to males for $AUC_{0\text{-}24h}$ and C_{max}, respectively.

Based on the results of this range finding study, the NOAEL for neonatal growth and developmental toxicity was 3 mg/kg/day.

2.2.2.2. A GLP 50-Day Oral (Gavage) Toxicity Study including TK with a 28-Day Recovery Period in Neonatal Sprague Dawley Rats (TE.701.TX.002)

The objectives of this study were to evaluate the potential effects of oral administration of tedizolid phosphate on neonatal growth, development, and fertility in male and female rats and to characterize the TK profile of tedizolid, the active moiety of tedizolid phosphate, when administered once daily for 50 consecutive days beginning on PND 7 through PND 56, followed by a 28-day recovery period.

Tedizolid phosphate, in the vehicle (25 mM disodium hydrogen phosphate buffered solution) was administered orally by gavage to 3 groups of male and female Sprague Dawley rats, obtained from nontreated time-mated females, once daily during PND 7 to 56. Initial dose levels were 1, 3, and 10 mg/kg/day for males and females; however, based on an age- and gender related decrease in exposure (AUC) observed at an intermediate TK evaluation conducted on PND 35, dose levels were increased to 4, 12, and 40 mg/kg/day for males and 2, 6, and 20 mg/kg/day for females beginning on PND 43 and continued through the remainder of the dosing period. A concurrent control group received the vehicle on a comparable regimen. The dose volume was 10 mL/kg for all groups. All groups consisted of 30 animals/sex.

Oral administration of tedizolid phosphate once daily at 10 mg/kg/day (high dose) to neonatal Sprague Dawley rats resulted in adverse effects, while no adverse effects were evident at the mid-dose (3/12 mg/kg/day in males and 3/6 mg/kg/day in females) and low-dose (1/4 mg/kg/day in males and 1/2 mg/kg/day in females) levels. The adverse effects at high dose included mortality and morbidity from

PND 17 to 24 (3 males and 1 female in main study group; 3 males and 1 female in the TK study group), clinical signs indicative of poor physical condition during PND 18 to 26, decreased body weight gain during PND 11 to 21, and lower mean body weight on PND 21 (approximately -17% vs. control). The group mean changes in body weight at the high dose were generally apparent before the mortality in individual animals. There was no adverse effect on food consumption. For males and females in the high dose group there was a non-adverse increase in food consumption during the latter part of the dosing period (PND 35 to 56) and during the recovery period. For the test article-related mortality at the high dose, 5 rats were found dead and 3 rats were euthanized. Adverse clinical findings in the high-dose group included pale body and cool or pale extremities noted during PND 18 to 26. In addition, partial closure of the eyes, increased respiration, shallow respiration, prostration, hypoactivity, gasping, and dermal atonia were noted generally on the day before or day of death or euthanasia. In 2 of the 8 rats either found dead or euthanized, there were no notable clinical signs.

There were test article-related hematology effects (decreases in total leukocytes, erythrocytes, hemoglobin, hematocrit [%], platelets, reticulocytes [absolute], absolute neutrophils, and absolute lymphocytes) noted in the 2 high-dose moribund male rats assessed for hematology before euthanasia. Compared with controls, mean neutrophil counts in peripheral blood were minimally lower in the low, mid, and high-dose males and mid and high-dose females at the primary necropsy. This change was accompanied by lower mean proportion of immature and mature myeloid precursors in the bone marrow on cytologic exam in the high dose (10/40 mg/kg/day group males and 10/20 mg/kg/day group females) animals. These changes were not present following the recovery period and were therefore reversible.

In the high dose group, there were no test article-related changes noted in ophthalmologic endpoints, postweaning developmental landmarks, FOB assessment, locomotor activity, auditory startle response, learning and memory, serum chemistry, urinalysis, peripheral blood cell phenotype, organ weight, gross pathology, or histopathology. No test article-related adverse effects were observed in the mid dose or low dose. In addition, no test article-related changes were observed for male and female reproductive organs, fertility parameters or indices at any dose level.

Based on these results, dose levels of 3/12 mg/kg/day (males) and 3/6 mg/kg/day (females) were identified as the NOAEL for overall toxicity. The average (based on TK measurements on PND 7, 35, and 56) plasma $AUC_{0\text{-}24h}$ value (sexes combined) was 30 µg* hr/mL. The adverse effects at the high dose occurred during the late pre-weaning and early post-weaning periods (from PND 11 to PND 26) and were no longer present during later portions of the treatment period. In addition, there were no test article-related effects during the recovery phase.

2.2.2.3. A GLP 50-Day Oral (Gavage) Toxicity Study with a 90-Day Recovery Period in Neonatal LE Rats (TE.701.TX.003)

The objectives of this study were to evaluate the potential effects of oral administration of tedizolid phosphate on neonatal growth and development (specifically development of the peripheral and central nervous system) in male and female LE rats as well as to verify exposure to tedizolid, the active moiety of tedizolid phosphate, when administered once daily for 50 consecutive days beginning on PND 7 through PND 56, followed by a 90-day recovery period.

This study was conducted in the LE strain of rat to complement the 9-month neurotoxicity study that was also conducted in the adult LE rat (Report No. TOX-11-07010028, previously submitted). As described below, this JAS in LE rats included special neuropathological evaluations of central and peripheral nervous tissue based on the objectives of the study. Comprehensive TK or routine pathology evaluations were not included as these endpoints were evaluated in the JAS in Sprague Dawley rats.

Tedizolid phosphate, in the vehicle (25 mM disodium hydrogen phosphate buffered solution) was administered orally by gavage to 3 groups of 20 male and 20 female LE rats, once daily during PND 7 to 56. Initial dose levels were 1, 3, and 10 mg/kg/day for males and females, however, based on an age- and gender-related decrease in exposure (AUC) observed in Sprague Dawley rats (see TE.701.TX.002), dose levels were increased to 4, 12, and 40 mg/kg/day for males and 2, 6, and 20 mg/kg/day for females beginning on PND 43 and continuing through the remainder of the dosing period. A concurrent control group composed of 20 males and 20 females received the vehicle on a comparable regimen. The dose volume was 10 mL/kg for all groups.

Oral administration of tedizolid phosphate once daily at 10 mg/kg/day (high dose) to neonatal LE rats was associated with adverse effects, while no adverse effects were evident at the mid- (3/12 mg/kg/day in males and 3/6 mg/kg/day in females) and low- (1/4 mg/kg/day in males and 1/2 mg/kg/day in females) dose levels tested. The adverse effects at the 10 mg/kg/day dose level included mortality and moribundity (eight rats) from PND 21 to 28, clinical signs of pale body and blue abdomen during PND 17 to 33, decreased body weight gain during PND 12 to 23, and lower mean body weights on PND 23. The decrease in group mean body weight gain was apparent beginning on PND 12, and therefore preceded the onset of mortality which was first noted on PND 21.

Clinical signs including labored respiration, body cool to the touch, and/or gasping were noted for some high-dose animals prior to death/euthanasia. Clinical findings noted in most of these animals included pale body and blue abdomen for several days prior to death or euthanasia. Although a cause of death could not be determined for the animals based on the macroscopic findings, the mortality and moribundity observed in the high dose group during PND 21 to 28 coincided with the time frame of presence of clinical signs (PND 17 to 33) and body weight effects (PND 12 to 23) in other high-dose animals. Test article-related mortality was not observed after PND 28. There were no test article-related clinical findings at the low- and mid-dose levels.

No test article-related effects on ophthalmologic examinations, FOB assessment, locomotor activity, auditory startle response, learning and memory, brain weight/measurements, and gross necropsy or microscopic pathology of central and peripheral nervous system tissue were noted in any dose group.

The findings observed in this JAS with LE rats were generally similar to the findings observed in the JAS with Sprague-Dawley rats. The sparse TK sampling in this LE rat study demonstrated that the 3 h post-dose plasma concentrations were similar to the 3 h post-dose plasma concentrations in the juvenile Sprague Dawley rats.

Based on these results, dose levels of 3/12 and 3/6 mg/kg/day were identified as the NOAELs for general toxicity in juvenile male and female LE rats, respectively. At these doses, mean PND 56 (end of dosing) plasma concentrations of tedizolid at 3 h post-dose were 5.27 and 6.45 µg/mL in males and females, respectively, which are similar to the concentrations achieved in juvenile SD rats at the same dose levels. Dose levels of 10/40 and 10/20 mg/kg/day were identified as a separate NOAEL for neurotoxicity in male and female LE rats, respectively. At these doses, mean PND 56 (end of dosing) plasma concentrations of tedizolid at 3 h post-dose were 15.3 and 12.3 µg/mL in males and females, respectively.

2.2.3. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) was submitted as part of the initial marketing authorisation application (MAA) for this Extension of indication, following the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2, 2006* and the *Questions and answers on Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016)* document.

ERA reports structure and requirements fulfil the relevant EU guidelines. The studies were conducted according to appropriate OECD test guidelines and under GLP conditions.

A comprehensible, concise and detailed ERA report for the active substance, consisted of Phase I and Phase II assessments. The relevant information required was given, and environmental risk was assessed based on the scientific discussion of the results obtained.

Relevant endpoints, methods used and results obtained were discussed and study results are summarised in the table below.

Substance (INN/Invented Name): Tedizolid phosphate				
CAS-number (if available): **856867-55-5**				
PBT screening		Result		**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	1.3		Potential PBT: N
PBT-assessment				
Parameter	**Result relevant for conclusion**			**Conclusion**
Bioaccumulation	log K_{ow}	< 3		Not B
Persistence	OECD 308 DT50 Wiehltalsperre Nordhafen	< 2 days at 12ºC		Not P
Toxicity	NOEC			Not T
PBT-statement :	Tedizolid is considered not PBT			
Phase I				
Calculation	***Value***		***Unit***	***Conclusion***
PEC_{sw}, default	1.0		µg/L	≥ 0.01 threshold: Y Phase environmental fate and effects analysis are needed.
Other concerns (e.g. chemical class)				N
Phase II Physical-chemical properties and fate				
Study type	**Test protocol**	**Results**		**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} = 2.6 L/kg 25ºC		Do not trigger value of 1000 L/kg OECD 106 study Koc for 2 sludges and 3 soils is needed
Ready Biodegradability Test	OECD 301B	2-7% biodegradation (14 days)		Not readily biodegradable
Aerobic Transformation in Sediment/Water System Sediment-system 1, Wiehltalsperre; Sediment-system 2, Nordhafen	OECD 308	Wiehltalsperre $DT_{50,\ water}$ < 2 day Total mass balance 102.8 Nordhafen $DT_{50,\ water}$ < 2 day Total mass balance 101.6 Radioactivity water phase: 0.6% Wiehltalsperre and 1.9% Nordhafen NER after 100 days Wiehltalsperre <5% with 12%		DT50s at 12°C Data at 100 day Tedizolid was removed rapidly from the water fraction and bound to the sediment in both sediment-systems.

		Nordhafen=12% Transformation products <10%			All transformation products detected in sediments were <10 % of the total radioactivity.
Phase IIa Effect studies					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test *(Raphidocelis subcapitata)*	OECD 201	EC10	0.098	mg/L	growth rate
Daphnia magna, Reproduction Test	OECD 211	EC10	1.1	mg/L	All end endpoints
Fish, Early Life Stage Toxicity Test (*Pimephales promelas*)	OECD 210	NOEC	0.021	mg/L	All end endpoints
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100	µg/L	Respiration
Phase IIb Studies					
Sediment dwelling organism (*Chironomus riparius)*	OECD 218	NOEC	≥100	mg/kg	28 days Corrected for 10% organic carbon

Phase I

The experimental log Dow values were determined using the OECD Guideline 117 HPLC method. A log Dow value of 1.3 was found, below the action limit of 4.5.

The MAH calculated the PECsurfacewater in compliance with the guideline on ERA EMEA/CHMP/SWP/4447/00 corr.2, 2006. The PECsurfacewater default value of 1.0 µg/L exceeds the action limit of 0.01 µg/L, so a Phase II environmental fate and effects analysis is required, according to the Guideline EMEA/CHMP/SWP/4447/00 corr 2, 2006.

Phase II – Tier A

Phase II is focused on obtaining data related to chronic ecotoxicological effects, biodegradation, potential for sorption to soil or sludge, and potential for partitioning to sediment of Tedizolid. The data from studies on aquatic species and sludge organisms are used to derive predicted no-effect concentrations (PNEC) for relevant environmental compartments according to the Guideline EMEA/CHMP/SWP/4447/00 Corr 2, 2006. Fate data can be used to assess transport within the environment and potential depletion mechanisms, and it may be used to derive predicted environmental concentrations. The more relevant methods were used, and the results were discussed.

The adsorption coefficient (Koc) was estimated according to the OECD 121 method. The log Koc values ranging from 1.5 to 5.0, are below the action limit of 10,000. The log Koc value reported by the OECD 121 method suggests that Tedizolid has low adsorption to sludge, but it is only an indicative value. The guideline EMEA/CHMP/SWP/4447/00 corr 2, 2006, asks for a batch equilibrium method (OECD 106 or OPPTS 835.1110), and since the HPLC method (OECD 121) is not a batch equilibrium method, it cannot replace batch equilibrium experiments. Thus, the batch equilibrium method (OECD 106) using two types of sludge and three soil types, which differ in organic carbon content and soil texture needed to be performed.

Based on the OECD 301B method, it has been determined that Tedizolid is not readily biodegradable, as no biodegradation was observed within 28 days.

Therefore, according to the Guideline EMA/CHMP/SWP/44609/2010 Rev.1, 2016, two naturally occurring aquatic sediment systems, that differed in pH and organic carbon content were studied to determine the fate of Tedizolid, according to the OECD Guideline 308. The half-lives at 20°C and extrapolated to 12°C (environmental temperature in Europe), in both aquatic systems are < 2 days. Tedizolid was removed rapidly from the water fraction and bound to the sediment in both sediment-systems (higher vs. lower organic carbon content). The amount of radioactivity in the water phase remained at 0.6% in Wiehltalsperre and 1.9% in Nordhafen. Non-extractable residues were in the sediment fraction of Wiehltalsperre with <5% and with 12% at Nordhafen after 100 days. All transformation products detected in both sediments were less than 10% of the total radioactivity.

Because of the lack of relevant biodegradation, the test item is assumed to accumulate in the sediment, and effects on a sediment-dwelling organism *Chironomus riparius* (OECD 218) were conducted.

The effects of algae, daphnia and fish were studied in accordance with OECD test guidelines and GLP. The predicted no-effect concentration (PNEC) values derived from laboratory studies were compared to the predicted environmental concentration (PEC) values.

The risk quotients ratios (PEC/PNEC) values presented for different environmental compartments (surface water, groundwater, and microorganisms) are well below the action limits indicating that the environmentally relevant residues of Tedizolid are of low risk for all compartments. Further testing in the aquatic compartment is unnecessary, as per the guidelines outlined in Guideline EMEA/CHMP/SWP/4447/00 Corr 2, 2006, and no risks were identified for Tedizolid.

Phase II – Tier B

The effects on a sediment dwelling organism *Chironomus riparus* were assessed according to (the OECD 218) method. Results from the sediment toxicity test, corrected for 10% organic content show that the NOEC is ≥ 100 mg/Kg. The risk (RQ) for sediment dwelling organisms is based on PECsediment (derived from PECsw) and PNECsed (derived from tests with sediment dwelling organisms). As the RQ for sediment dwelling organisms is <1, this meets the Guideline requirement for no further testing of Tedizolid in sediment.

Appropriate disposal of unused pharmaceuticals is considered important to reduce the exposure of the environment. Precautionary and safety measures taken to reduce the risk to the environment, and enhance environmental protection, on SmPC and PL were applied by the MAH, according to "*Guideline on the environmental risk assessment of medicinal products for human use*" (EMEA/CHMP/SWP/4447/00 corr 2, 2006).

Since the revised guideline on the ERA of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.) came into force on 1 September 2024, a conclusion on the risks in groundwater, soil and to predators consuming contaminated prey (secondary poisoning) will have to be included in the ERA. The updated ERA can be provided together with the completed OECD 106 study report.

2.2.4. Discussion on non-clinical aspects

Comprehensive non-clinical toxicology evaluations were previously submitted in support of the original marketing application for ABSSSI in adults as well as the supplemental application in adolescents (≥12 to <18 years of age), including PO and IV repeat-dose toxicology in rats (up to 6 months) and dogs (up to 1-month), in vitro and in vivo genotoxicity, as well as oral reproductive and developmental toxicity in mice, rats, and rabbits. Other studies were conducted for local tolerance, immunotoxicity, phototoxicity,

neuropathology, and impurity qualifications. Carcinogenicity studies were not conducted given the short clinical exposure duration.

Considering the previous studies, the hematopoietic and the gastrointestinal systems were the primary targets following PO and IV repeat dose administration of tedizolid phosphate at generally tolerated doses, with these effects showing evidence of reversibility and occurring at multiples of the human tedizolid therapeutic exposure level.

Three JAS in rats conducted after the original marketing application are included in the dossier in support of this paediatric extension of indications application. They were conducted in accordance with the PIP agreed with the EMA and the PSP agreed with the FDA. The MAH clarified that the developmental age of rats in the neonatal toxicity studies covers the intended paediatric age range from birth to <12 years of age. The justification resides on the following assumptions: since rats are immature at birth, a rat pup that is 4 to 7 days of age is considered developmentally like a preterm infant and, in addition, a rat 9 to 10 days of age generally corresponds to a human term neonate.

The GLP JAS identified no specific, nor unique target organs of toxicity compared to those already identified in the repeat oral dose toxicity studies in adult rats at generally tolerated doses. Additionally, the primary target organ of toxicity in the JAS studies appear to be limited to the hematopoietic system. Similarly to studies in adult rats, mortality was associated with weight loss (likely gastrointestinal related) and clinical signs were observed at higher non-tolerated doses/exposures.

After oral administration of tedizolid phosphate to juvenile rats from PND 7 through 56, no effects on reproductive systems or the peripheral or central nervous systems were noted. There were no effects on postweaning development landmarks, learning and memory, or neurobehavioral assessments at any of the tested doses in either definitive GLP JAS. At the highest dose (10/40 mg/kg/day in males, 10/20 mg/kg/day in females) in the Sprague Dawley rat JAS, poor tolerability (adverse clinical signs, body weight loss, and mortality) was observed between PND 11 to 26 These adverse systemic effects were not observed with continued dosing during the later portions of the dosing phase, and no effects were present during the recovery phase of the study.

The NOAEL (3/12 mg/kg/day for males; 3/6 mg/kg/day for females) in the neonatal study in Sprague-Dawley rats (TE.701.TX.002) corresponded to a sexes combined average $AUC_{0\text{-}24h}$ of 30 µg*hr/mL. In comparison, the NOAEL (30 mg/kg/day for males; 10 mg/kg/day for females) in the 28-Day Repeat Oral Dose Toxicity Study in Rats (Report No. TOX-07-0701-014A, previously submitted) corresponded to a sex combined Study Day 28 $AUC_{0\text{-}24h}$ of 67.8 µg* hr/mL. Therefore, the NOAEL in the neonatal study was approximately 2-fold lower compared to the NOAEL in 28-day study with older rats. The clinical steady state AUC values in pediatric patients from birth to <12 years of age ranged from 22.5 to 38.7 µg*hr/mL, similar to the exposures at the NOAEL in the JAS in rats.

Notwithstanding the above, the following is considered necessary to address the ERA: the completed OECD 106 study report, including an updated ERA should be submitted. Since the revised guideline on the ERA of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.) came into force on 1 September 2024, the MAH was asked to include in the ERA a conclusion on the risks in groundwater, soil and predators consuming contaminated prey (secondary poisoning).

2.2.5. Conclusion on the non-clinical aspects

The results from the presented new non-clinical studies are generally aligned with the nonclinical safety profile of tedizolid phosphate identified for the previously approved indication in adults and adolescents (≥12 to <18 years of age) and do not raise any additional concerns from the non-clinical perspective.

The following text has been added to Section 5.3 of the SmPC:

In studies in juvenile rats, no specific, nor unique target organs of toxicity were observed compared to those already identified in the repeat oral dose toxicity studies in adult rats. However, the exposure at the no observed adverse effect level (NOAEL) (based on AUC_{0-24h}) of the juvenile toxicity study was 2-fold lower compared to the exposure in the 28-day study in adult rats. Accordingly, plasma exposure levels in the juvenile toxicity study were similar to those in paediatric patients at the human therapeutic dose.

Since the revised guideline on the ERA of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.) came into force on 1 September 2024, a conclusion on the risks in groundwater, soil and to predators consuming contaminated prey (secondary poisoning) will have to be included in the ERA. The updated ERA can be provided together with the completed OECD 106 study report.

The MAH provided a letter including a timetable describing when the studies will be completed.

2.3. Clinical aspects

2.3.1. Introduction

PK, efficacy, and clinical safety results for tedizolid phosphate from 2 Phase 1 and 1 Phase 3 clinical studies in support of the extension of the indication for use in patients <12 years of age with ABSSSI are summarised below in this report.

An overview of P013, P014, and P018 studies is provided in the following table:

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Dosing Regimen[a,b]	Study Population (N)[c]	Primary Objective(s)
Phase 3 Study (Participants <12 Years)				
P018 (Completed) [Ref. 5.3.5.1: P018MK1986] 20 sites (4 regions)	Randomized (tedizolid phosphate: comparator 3:1), assessor-blind, active-controlled, multicenter, parallel-group, intervention study Indication: ABSSSI	Tedizolid phosphate (n=75) for 6 to 10 days[d] IV and/or PO: once daily 200 mg (body weight ≥50 kg), q12h 2 mg/kg (body weight ≥30 to <50 kg), q12h 2.5 mg/kg (body weight ≥3.2 to <30kg). Comparator (n=25) for 10 to 14 days[d] IV and/or PO from	Gender: 53M/47F Age: 28 days to <12 years N=100 in the following age groups: 6 to <12 years (n=59) 2 to <6 years (n=21) 28 days to <2 years (n=20) From birth to <28 days (none enrolled in this planned cohort) Participants with ABSSSI	To evaluate the safety of IV and/or PO 6- to 10-day tedizolid phosphate with 10- to 14-day IV and/or PO comparator in participants from birth to <12 years of age with ABSSSI. No formal hypothesis tests will be used to evaluate this endpoint.

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Dosing Regimen[a,b]	Study Population (N)[c]	Primary Objective(s)
		allowed list per local standard of care (per product labeling)[e]		

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Dosing Regimen[a,b]	Study Population (N)[c]	Primary Objective(s)
Phase 1 Studies (Participants <12 Years)				
P013 (Completed) [Ref. 5.3.3.2: P013MK1986] 15 sites (3 regions)	Nonrandomized, open-label, uncontrolled, multicenter, 2-part, SD study Indication: Bacterial infection (no efficacy endpoints)	Tedizolid phosphate SD IV: 6 to <12 years: 5 mg/kg (n=5) or 4 mg/kg (n=5) 2 to <6 years: 6 mg/kg (n=5) or 3 mg/kg (n=5) Tedizolid phosphate SD PO: 6 to <12 years: 4 mg/kg (n=6) 2 to <6 years: 3 mg/kg (n=6)	Gender: 19M/13F Age: 2 to <12 years N=32 in the following age groups: 6 to <12 years (n=16) 2 to <6 years (n=16) Hospitalized participants receiving prophylaxis for or with a confirmed or suspected infection with gram-positive bacteria and receiving concurrent antibiotic treatment with gram-positive antibacterial activity	Part A (IV Study Intervention Administration): To describe the single-administration PK of IV tedizolid phosphate and its active metabolite, tedizolid, in participants aged 6 to <12 years (Group 1) and 2 to <6 years (Group 2). Part B (PO Study Intervention Administration): To describe the bioavailability of tedizolid following PO tedizolid phosphate administration to participants aged 6 to <12 years (Group 3) and 2 to <6 years (Group 4).

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Dosing Regimen[a,b]	Study Population (N)[c]	Primary Objective(s)
P014 (Completed) [Ref. 5.3.3.2: P014MK1986] 17 sites (3 regions)	Nonrandomized, open-label, uncontrolled, multicenter, 2part, SD and MD, intervention study Indication: Bacterial infection (no efficacy endpoints)	Tedizolid phosphate 3 mg/kg (body weight <10 kg) or 2.5 mg/kg (body weight 10 to <30 kg): SD IV: 28 days to <6 months (n=4) 6 months to <24 months (n=6) From birth to <28 days: Full-term neonates (n=8) Preterm neonates (n=9) MD IV twice daily for 3 days: From birth to <28 days: Full-term neonates (n=4) Preterm neonates (n=4) SD PO: 28 days to <24 months (n=4) From birth to <28 days: Full-term neonates (n=4) Preterm neonates (n=4)	Gender: 29M/18F Age: Birth to <24 months N=47 in the following age groups: 28 days to <24 months (n=14) From birth to <28 days: Full-term neonates (n=16) Preterm neonates (n=17) Hospitalized participants receiving prophylaxis or treatment for a confirmed or suspected infection with gram-positive bacteria	To describe the SD PK of IV tedizolid phosphate and its active metabolite, tedizolid, when administered to paediatric participants aged 28 days to <24 months (Group 1 [Cohorts 1 and 2 combined]), full-term neonates aged birth to <28 days (Group 2), and preterm neonates aged birth to <28 days (Group 3). To describe the MD PK of IV tedizolid phosphate and its active metabolite, tedizolid, when administered to full-term neonates aged birth to <28 days (Group 2) and preterm neonates aged birth to <28 days (Group 3). To describe the SD PK of tedizolid following PO suspension of tedizolid phosphate administration to paediatric participants aged 28 days to <24 months (Group 4), full-term neonates aged birth to <28 days (Group 5), and preterm neonates aged birth to <28 days (Group 6).

ABSSSI=acute bacterial skin and skin structure infection; CTD=Common Technical Document; EU=European Union; F=female; IAs=interim analyses; IV=intravenous; M=male; M&S=modeling and simulation; MD=multiple-dose; MK1986=tedizolid phosphate (SIVEXTRO™); N=number of participants who received ≥1 dose of study intervention in the study; n=number of participants in the age cohort who received ≥1 dose of study intervention in the dosing regimen or age group; PK=pharmacokinetic(s); PO=oral; q12h=every 12 hours; SD=single-dose.

[a] For all studies, IV doses were administered as an IV infusion over approximately 1 hour.

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Dosing Regimen[a,b]	Study Population (N)[c]	Primary Objective(s)

[b] Dose modifications were performed during the studies based on PK IAs and M&S analyses.

[c] Age is at time of consent. Participants 28 days to <2 years of age were preterm or full-term at birth. Full-term neonates were born ≥37th week of gestation. Preterm neonates were born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

[d] In P018, treatment duration could have been prolonged up to a maximum of 10 days of tedizolid phosphate or 14 days of comparator, if clinically indicated based on blinded investigator assessment at Visit 4 (~Day 6 of dosing) in the tedizolid group or Visit 5 (~Day 10 of dosing) in the comparator group.

[e] Allowed IV comparators in P018 were vancomycin, linezolid (outside the EU only, as it is not approved for paediatric use in the EU), clindamycin, flucloxacillin, and cephazolin (cefazolin). Allowed oral comparators were linezolid (outside the EU only), clindamycin, flucloxacillin, and cephalexin (cefalexin).

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

The PK of tedizolid following IV or oral dosing of tedizolid phosphate in support of the adult and the adolescent indication is described in the prescribing information. A summary of the ADME and clinical pharmacology established in adults and adolescents is provided below. The dosing proposed for the paediatric population is based on attaining generally similar tedizolid exposures to the adult population which justifies the applicability of the conclusions derived in the adult population to the paediatric population (birth to <12 years of age) described in this submission.

Absorption

Peak plasma tedizolid concentrations are achieved within approximately 3 hours following oral administration under fasting conditions or at the end of the 1 hour intravenous infusion (Ceoi) of tedizolid phosphate. The absolute bioavailability is approximately 91% and no dosage adjustment is necessary between IV and oral administration.

Tedizolid phosphate (oral) may be administered with or without food as total systemic exposure is unchanged between fasted and fed (high-fat, high-calorie) conditions.

Distribution

Protein binding of tedizolid to human plasma proteins is approximately 70% to 90%. The mean steady state volume of distribution of tedizolid in healthy adults following a single intravenous dose of tedizolid phosphate 200 mg ranged from 67 to 80 L (approximately twice total body water). Tedizolid penetrates the interstitial space fluid of adipose and skeletal muscle tissue with exposure similar to free drug exposure in plasma.

Elimination

Tedizolid phosphate is converted by endogenous plasma and tissue phosphatases to the microbiologically active moiety, tedizolid. Other than tedizolid, which accounts for approximately 95% of the total radiocarbon AUC in plasma, there are no other significant circulating metabolites in humans following a single oral dose of ^{14}C-labeled tedizolid.

When incubated with pooled human liver microsomes, there was no degradation of tedizolid suggesting that tedizolid is not a substrate for hepatic CYP450 enzymes. Multiple SULT enzymes (SULT1A1, SULT1A2, and SULT2A1) are involved in the biotransformation of tedizolid, to form an inactive and noncirculating sulphate conjugate found in the excreta.

Tedizolid is eliminated in excreta, primarily as a non-circulating and microbiologically inactive sulphate conjugate. Following single oral administration of ^{14}C-labeled tedizolid phosphate under fasted conditions, the majority of elimination occurred via the liver with 81.5% of the radioactive dose recovered in faeces and 18% in urine, with most of the elimination (>85%) occurring within 96 hours. Less than 3% of tedizolid phosphate administered dose is excreted as active tedizolid. The elimination half-life of tedizolid is approximately 12 hours and the intravenous clearance is 6 to 7 L/h.

Dose proportionality and time dependencies

Tedizolid demonstrated linear pharmacokinetics with regard to dose and time. The C_{max} and AUC of tedizolid increased approximately dose proportionally within the single oral dose range of 200 mg to 1,200 mg and across the intravenous dose range of 100 mg to 400 mg. Steady state concentrations are achieved within 3 days and indicate modest active substance accumulation of approximately 30% following multiple once daily oral or intravenous administration as predicted by a half-life of approximately 12 hours.

No dosage adjustment of tedizolid phosphate is required in renally impaired and/or hepatically impaired patients. No dosage adjustment of tedizolid phosphate is required based on gender or race of the patients.

Tedizolid Pharmacokinetics in Adult and Adolescent Populations

Tedizolid phosphate is approved as a 200-mg tablet (administered once daily) and as a vial for IV infusion (administered over 1 hour once daily) for adults and adolescents aged ≥12 years. The biopharmaceutical properties of the IV and tablet formulations have been described in previously approved applications.

The development program for the paediatric population <12 years of age included 3 (2 Phase 1 and 1 Phase 3) clinical studies. The 2 Phase 1 studies, MK-1986-013 (P013) and MK-1986-014 (P014), evaluated the PK and tolerability of single oral and IV doses of tedizolid phosphate in participants aged 2 to <12 years and <2 years, respectively. Multiple-dose neonatal (full-term and preterm neonates <28 days of age) cohorts were also included in P014 to evaluate the tolerability and PK of tedizolid phosphate IV in this age group. The Phase 3 study, MK-1986-018 (P018), evaluated the safety and efficacy of multiple doses of oral and IV tedizolid phosphate in participants <12 years of age. The clinical program was designed to provide safety data in the paediatric population <12 years to permit bridging from adolescents and adults, descriptive evaluation of efficacy from P018, and PK data as a basis of extrapolation of efficacy. Initial dose selection for each of the clinical trials included in this application (P013, P014, and P018) was intended to achieve similar exposure (AUC) of tedizolid in participants <12 years of age to adults and enable the bridging of safety and extrapolation of efficacy. Previously, PK/PD infection model studies identified the drug exposure targets (i.e., PK/PD indices) that are most closely associated with therapeutic outcomes of interest and were used to support the original adult marketing

application. The fAUC/MIC ratio, primary index of efficacy, for tedizolid to achieve stasis in immunocompetent mice was approximately 3, which would correspond to a total AUC/MIC ratio of approximately 15 to account for protein binding of approximately 70% to 90%. A >90% PTA was achieved at the 200-mg dose of tedizolid phosphate for adult and adolescent participants with ABSSSI and a MIC value of 0.5 µg/mL. As tedizolid inhibits an exogenous target, and the pathogens responsible for ABSSSI are similar regardless of age group, the bacterial response to tedizolid is not expected to be influenced by the age of the patient. Considering this, and the PK/PD target summarized above, tedizolid exposures that have been shown to be generally safe and efficacious in adults were expected to provide similar PD effects in paediatric patients independent of patient age. The clearance of tedizolid was not expected to be meaningfully different in paediatric participants compared with adults and adolescents when weight was considered, which was achieved by weight-based dosing. Thus, the intent of dose selection in the paediatric studies informing the present application (P013, P014, and P018) was to achieve similar AUCs compared to the adults. Given that there have been no safety concerns to inform an upper limit for exposure, the critical consideration was attainment of tedizolid exposures resulting in a high probability of antibacterial efficacy, maximizing clinical benefit.

Phase 1 (Study P013) – Paediatric Safety and PK Study – Single administration of Oral and IV Tedizolid Phosphate in Participants 2 to <12 Years of age

This was an open-label, multicenter, 2-part, single dose study to assess the PK of tedizolid following administration of a single IV infusion (Table 2) or a single oral dose of tedizolid phosphate administration (Table 3) to hospitalized participants ages 2 to <12 years. A total of 32 participants received a single dose of tedizolid phosphate: 20 participants received a single IV infusion and 12 participants received a single oral dose based on the weight. Participants aged 6 to <12 years receiving a single tedizolid phosphate IV infusion were dosed with 4 mg/kg or 5 mg/kg and participants receiving a single oral dose were given 4 mg/kg. Participants aged 2 to <6 years receiving a single tedizolid phosphate IV infusion were dosed with 3 mg/kg or 6 mg/kg and participants receiving a single oral dose were given 3 mg/kg.

Exposure distributions at the different weight-based doses and the route of administration (a single IV infusion or a single oral dose) were evaluated. Following a single IV infusion of tedizolid phosphate administered to participants 2 to <12 years of age, peak tedizolid plasma concentrations were reached approximately at the end of the 1-hour infusion period. The tedizolid terminal half-life (geometric mean) ranged from approximately 4.93 to 5.76 hours among participants in the IV groups. Following a single oral dose of tedizolid phosphate to participants 2 to <12 years of age, peak tedizolid plasma concentrations were achieved between 2 to 3 hours. The tedizolid terminal half-life (geometric mean) was 6.15 hours and 6.79 hours in the 6 to <12 years and 2 to <6 years of age groups, respectively. Results from a non-compartmental analysis can be seen in Table 1.

Table 1. Summary Statistics of Tedizolid Pharmacokinetic Parameters Following the Administration of Single IV or Oral Doses of Tedizolid Phosphate, Presented as GM and 95% CI (PK Population)

Pharmacokinetic	Group 1 Cohort 1 (6 to <12 years) 5mg/kg (IV) (N = 5)		Group 1 Cohort 2 (6 to <12 years) 4mg/kg (IV) (N = 5)		Group 2 Cohort 1 (2 to <6 years) 6mg/kg (IV) (N = 5)		Group 2 Cohort 2 (2 to <6 years) 3mg/kg (IV) (N = 5)		Group 3 (6 to <12 years) 4mg/kg (oral) (N = 6)		Group 4 (2 to <6 years) 3mg/kg (oral) (N = 6) ††	
Parameters	GM	95% CI	GM	95% CI	GM	95% CI	GM	95% CI	GM	95% CI	GM	95% CI
$AUC_{0\text{-last}}$ (hr*ng/mL) †	28200	(21200, 37600)	19700	(14800, 26200)	26800	(20200, 35800)	17100	(12800, 22700)	22700	(17500, 29500)	14600	(11200, 18900)
$AUC_{0\text{-}\infty}$ (hr*ng/mL) †	29600	(22500, 38900)	21000	(16000, 27600)	27300	(20800, 35900)	17300	(13200, 22700)	24900	(19400, 32000)	17200	(13100, 22600)
C_{max} (ng/mL) †	4960	(3440, 7140)	4140	(2880, 5970)	7460	(5180, 10800)	4190	(2910, 6030)	2590	(1860, 3620)	1820	(1310, 2550)
T_{max} (hr) ‡	1.18	(1.07, 1.50)	1.10	(1.00, 1.33)	1.12	(1.07, 1.17)	1.00	(1.00, 1.05)	2.53	(1.20, 6.02)	3.08	(3.00, 12.00)
Apparent $t_{1/2}$ (hr) §	5.18	21.54	4.93	13.82	5.51	30.16	5.76	29.20	6.15	24.41	6.79	10.85
CL/F (mL/hr/kg) §‖	4164.60	36.39	4145.73	73.21	2582.66	20.64	2461.08	11.99	4073.32	21.14	2090.77	50.27
Vd/F (mL/kg) §¶	31129.20	20.56	29466.90	72.97	20517.55	35.10	20435.88	29.37	36167.24	34.73	20491.01	62.49

† Back-transformed least squares mean and confidence interval from linear fixed effects model performed on natural log-transformed values.

‡ Median (min, max) reported for Tmax.

§ Geometric mean and percent geometric coefficient of variation reported for apparent $t_{1/2}$, CL/F and Vd/F.

‖ CL for IV and CL/F for Oral, where F is bioavailability.

¶ Vd for IV and Vd/F for Oral, where F is bioavailability.

†† N=5 for $AUC_{0\text{-}\infty}$, apparent $t_{1/2}$, CL/F and Vd/F.

Square root of conditional mean squared error (residual error) from the linear fixed effects model = 0.312 for $AUC_{0\text{-last}}$, 0.297 for $AUC_{0\text{-}\infty}$ and 0.397 for C_{max}. When multiplied by 100, provides estimate of the pooled between-subject coefficient of variation.

GM = Geometric least-squares mean; CI = Confidence interval.

Phase 1 (Study P014) – Paediatric Safety and PK Study– Single and Multiple Dose Administration of Oral and IV Tedizolid Phosphate in Participants Birth to <24 Months of age

This was an open-label, multicenter, single and multiple dose study to assess the PK, safety, and tolerability of tedizolid phosphate in hospitalized participants aged birth to <24 months receiving prophylaxis or treatment for a confirmed or suspected infection with gram-positive bacteria. The starting dose of tedizolid phosphate in this study was 3 mg/kg administered as a single dose for participants aged 28 days to <24 months. After an interim analysis, the tedizolid phosphate doses expected to achieve comparable tedizolid exposures across the weight stratification and when compared to adult exposures were 3.0 mg/kg (body weight <10 kg) and 2.5 mg/kg (body weight 10 to <30 kg) when administered twice daily either as an IV infusion or as oral dose. In P014, 3 preterm neonates received 3 mg/kg oral suspension administered via a nasogastric tube. Of the total 47 participants enrolled in the study, 40 participants had measurable tedizolid concentrations and were considered evaluable for PK analysis. Accounting for variability and imbalances in sample size across each of the age groups, tedizolid exposure (AUC, Cmax) was generally comparable after administration of a single IV infusion or a single oral dose of tedizolid phosphate. Although data were more limited, steady-state tedizolid exposure (Cmax,ss, AUC0-12,ss) after multiple IV infusions of tedizolid phosphate appeared to be largely similar across full-term and preterm neonates. Tedizolid exposure after single- vs multiple-dose administration was also comparable, indicating minimal accumulation. The multiple doses of tedizolid phosphate were generally well tolerated.

Table 2 - Summary Statistics of Tedizolid Pharmacokinetic Parameters Following Administration of a Single IV Infusion of Tedizolid Phosphate to Participants Aged 28 Days to <24 Months (Group 1 Cohort 1 and Cohort 2), Full-term Neonates (Group 2 Cohort 1), and Preterm Neonates (Group 3 Cohort 1)

Pharmacokinetic Parameters	28 days to <24 months (Group 1 Cohort 1 and 2)			Full-term neonates (Group 2 Cohort 1)			Preterm neonates (Group 3 Cohort 1)		
	N	GM (95% CI)	% CV [d]	N [e]	GM (95% CI)	% CV [d]	N [f]	GM (95% CI)	% CV [d]
AUC0-24 (hr*ug/mL) [a]	10	13.6 (10.2, 18.2)	42.4	5	8.23 (2.62, 25.9)	115.9	3	15.6 (10.1, 24.1)	17.6
AUC0-inf (hr*ug/mL) [a]	10	14.3 (10.8, 18.9)	40.4	5	9.21 (2.71, 31.3)	128.2	3	17.8 (10.7, 29.7)	20.9
Cmax (ug/mL) [a]	10	2.19 (1.55, 3.09)	51.0	6	0.962 (0.489, 1.89)	71.9	5	1.35 (0.798, 2.29)	44.5
Tmax (hr) [b]	10	1.33 (1.00, 1.58)		6	1.41 (1.00, 2.50)		5	1.50 (1.08, 6.53)	
$t1/2$ (hr) [c]	10	4.17 (47.7)		5	6.63 (38.0)		3	7.08 (41.2)	
CL (mL/hr) [c]	10	1270 (63.3)		5	835 (148.6)		3	347 (51.9)	
Vz (mL) [c]	10	7620 (84.6)		5	7990 (106.3)		3	3540 (14.3)	

[a] Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[b] Median (min, max) reported for Tmax.
[c] Geometric mean and percent geometric coefficient of variation.
[d] % CV is square root of corresponding estimated variance obtained for each population in fixed effect model multiplied by 100.
[e] AUC0-inf, AUC0-24, $t1/2$, CL and Vz could not be calculated for one participant.
[f] AUC0-inf, AUC0-24, $t1/2$, CL and Vz were not included in the analysis when AUC0-inf % extrapolated >50%.

CI = Confidence interval, CV = Coefficient of variation, GM = Geometric least-squares mean, IV = Intravenous.

Table 3 - Naïve-Pooled Summary Tedizolid Plasma Pharmacokinetics Following Administration of a Single Oral Dose of Tedizolid Phosphate to Participants Aged 28 Days to <24 Months (Group 4), Full-term Neonates (Group 5), and Preterm Neonates (Group 6)

Pharmacokinetic Parameter	28 days to <24 months (Group 4) [a, c]	Full-term neonates (Group 5) [d]	Preterm neonates (Group 6) [c]
AUC0-24 (hr*µg/mL)	7.92	9.25	14.9
AUC0-inf (hr*µg/mL)	8.36	9.44	22.1
Cmax (µg/mL)	1.32	0.899	1.22
Tmax (hr)	1	3.03	8
t1/2 (hr)	5.73	3.82	13.4
wnCL/F (mL/hr/kg) [b]	295	261	111
wnVz/F (mL/kg) [b]	2440	1440	2150
F	58.5	103	124

[a] One participant in Group 4 received 2.5 mg/kg.
[b] Weight normalized parameters were determined based on a dose of 3 mg/kg.
[c] Naive pooled PK parameters based on N=3.
[d] Naive pooled PK parameters based on N=4.

wn = Weight normalized.

Phase 3 (Study P018) – Safety and Efficacy study– Multiple Dose Administration of Oral and IV Tedizolid Phosphate in Participants Birth to <12 Years of age

This study was a randomized (3:1 ratio), active controlled, assessor blinded, multicenter, multiple dose Phase 3 study to assess the safety and efficacy of tedizolid phosphate (IV and/or oral) versus protocol-specified active comparators (IV and/or oral) for the treatment of ABSSSI in participants aged birth to <12 years. The study enrolled participants aged 28 days to <12 years; no participants aged <28 days were enrolled in the study. Overall, 75 participants were enrolled to receive tedizolid phosphate (44 participants aged 6 to <12 years, 16 participants aged 2 to <6 years, and 15 participants aged 28 days to <2 years). Out of the 75 participants enrolled in the study, 73 participants had measurable tedizolid concentrations and were considered evaluable for PK analysis.

The protocol permitted dosing adjustments in P018 based on accruing data from the paediatric program. The adjustments were intended to optimize the dosing regimen that would result in similar exposures in participants aged <12 years when compared to systemic exposures previously determined in adults. Based on a preliminary population PK model, the starting dosing regimens for P018 were once daily 200

mg (body weight ≥40 kg) and twice daily 3 mg/kg (body weight <40 kg). Following interim analyses, the doses of tedizolid phosphate were revised to the following: once daily 200 mg (body weight ≥50 kg), twice daily 2 mg/kg (body weight 30 to <50) and twice daily 2.5 mg/kg (body weight 3.2 to <30 kg).

Sparse PK samples were collected in this study to support the development of a paediatric population PK model. Within the study, pre-dose plasma concentrations at steady state for tedizolid were generally comparable across the route of administration (IV and oral) and across the weight-based doses for each age cohort (6 to <12 years, 2 to <6 years and 28 days to <2 years).

Population Pharmacokinetic Analysis

A population PK modelling approach was used to evaluate tedizolid PK in participants aged birth to <18 years of age by developing a paediatric population PK model (also referred to as the 'paediatric model') specifically utilizing the PK from only the paediatric studies by integrating all available PK data in paediatric participants <18 years of age. The paediatric population PK analysis was performed by re-estimating the previously developed adolescent population PK model to a merged dataset containing the combined data from P026, P012, P013, P014, and P018. Data from P026 and P012 were already reflected in the analysis dataset, as these data were used in the previous adolescent population PK model. As such, new data reflected those from studies P013 (2 to <12 years of age), P014 (birth to < 2 years of age), and P018 (28 days to <12 years of age).

A total of 1418 concentration records collected from 154 participants enrolled in Studies P013, P014, and P018 were included in the source datasets received from Merck. Consistent with the objective of the PK analysis and considering that prodrug TZP is rapidly and completely converted to the active moiety (TZD), TZP concentration records (N = 686) were not included in the analysis dataset.

In Study P013, a total of 3 samples were excluded due to missing concentration values and 1 sample was excluded due to missing sample date/time. In Study P014, a total of 18 samples were excluded due to BLQ concentration values. In Study P018, a total of 45 samples were excluded as not done/not recorded, and 5 samples were excluded due to BLQ concentration values. During the course of exploratory data analysis and initial base PK model development, 10 PK samples (6 samples from Study P014 and 4 samples from Study P018) were identified as outlier concentrations and excluded from the analysis. These concentrations were flagged as outliers because the observed concentration represented an unusual increase/decrease relative to the surrounding concentrations at nearby times since previous dose relative to the remaining data for this participant and compared to pooled concentration data from the participant population in the respective study. Additionally, data from 4 participants from Study P014 were identified as having outlying (very low) concentrations in their entirety relative to observed data in the remainder of the study population. These concentrations were collected following multiple dosing and were several orders of magnitude lower than observed drug concentrations in the rest of the participant population in Study P014; a review of these concentration-time profiles, relative to the remainder data in the study population, indicated that the profiles were biologically implausible. Thus, these 4 participants were completely excluded from the analysis.

The analysis dataset included 1191 tedizolid plasma concentration records from 249 participants. The analysis dataset also included information regarding the gestational age for the neonatal population in P014 which allowed for evaluation of PMA as a covariate to account for the maturation of the metabolic enzymes in the younger participants.

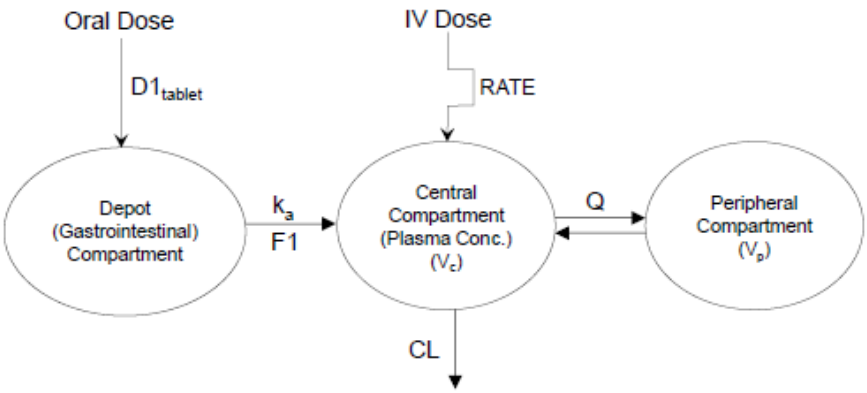
The tedizolid population PK analysis data encompassed single- and multiple-dose (twice daily and once daily) regimens of tedizolid phosphate, administered via nominal 60-minute IV infusions or orally as either tablet or oral suspension formulations. Tedizolid phosphate was administered as either fixed 200

mg IV or tablet doses, or as body weight-based (mg/kg) IV or oral suspension doses ranging from 2 to 6 mg/kg. Overall, the paediatric population PK model was used to estimate tedizolid PK parameters, to assess the influence of pertinent intrinsic factors (including age, body weight, IBW, race, renal function [eGFR], and liver function [total bilirubin]) on tedizolid PK, to obtain empiric Bayesian PK parameter estimates (post hoc) to predict individual tedizolid exposures for use in PTA and E-R analyses, and to perform stochastic simulations to comprehensively explore and critically evaluate potential weight-banded dose regimens.

The analysis dataset included 22 neonates (12 preterm neonates and 10 full-term neonates < 28 days old). A preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation; a full-term neonate is defined as an infant born ≥ 37th week of gestation. There were 28 participants who were 28 days to < 2 years of age, 31 participants who were 2 to < 6 years of age, 60 participants who were 6 to < 12 years of age, and 108 participants who were 12 to ≤ 18 years of age included in the analysis. Gestational age and PMA were only available in participants from Study P014, with a median (range) gestational age of 38 (26.6 to 41) weeks and a median (range) PMA of 9.30 (6.6 to 28.2) months. The analysis population was comprised predominantly of white subjects (80.7%), while 10.8% were black/African American and 7.63% of population were characterized as "multiple or other" race. Males and females comprised 61% and 39% of the analysis population, respectively. The overall median (range) age and weight of the population were 9 (0 to 18) years and 34 (1.0 to 126.3) kg, respectively.

Tedizolid PK were adequately described by a 2-compartment model with zero-order input for IV infusions, first-order absorption for oral suspension doses, and sigmoidal absorption for tablet doses (including separate bioavailability estimates for oral suspension and tablet formulations), and linear elimination, consistent with the PK in adults and adolescents ≥ 12 years of age (Figure 1). The sigmoidal model was ideal for describing absorption from tablets, as it enabled a better characterization of the delay in observed tedizolid plasma concentrations due, in part, to the dissolution of prodrug tedizolid phosphate from the tablet formulation prior to absorption as well as the metabolic conversion of tedizolid phosphate to tedizolid.

Figure 1 - Schematic of the Population Pharmacokinetic Model Structural Form for Tedizolid



Abbreviations: CL, clearance; Conc, concentration; D1, duration of zero-order input for tablet dose; F1, absolute bioavailability of oral suspension and tablet doses; IV, intravenous; k_a, first-order absorption rate constant for oral dose; Q, distributional clearance; RATE, rate of intravenous infusion; V_c, central volume of distribution; V_p, peripheral volume of distribution.

During population PK model development, the methodology for allometric scaling was thoroughly assessed to best characterize the influence of body size on the disposition of tedizolid. Of note, at very

young ages (that is, neonates and infants), the capacity of eliminating organs is a dynamic evolving process, with maturation of elimination processes closely correlated with age. Gestational age and PMA represent commonly used age markers to model and describe the maturation process. However, none of the maturation functions that were tested in the model contributed to a meaningful improvement in the estimated Bayesian estimates for CL or predictions of tedizolid concentrations in the neonate population, suggesting that allometric scaling was sufficient to adequately characterize the elimination of tedizolid in this subpopulation.

Identification of significant covariates was based on step-wise forward addition ($p<0.05$) and backward elimination ($p<0.005$) using the SCM process. As some covariates evaluated in the SCM are correlated, potentially marginal covariates that were identified as significant were further evaluated to confirm that their inclusion improved model fit.

The final population PK model included estimated exponents for allometric body weight scaling on CL (and Q) and Vc (and Vp). Each of these parameter-covariate relationships was described according to a power function, centered on the median observed body weight (34 kg) in the analysis population. The final paediatric population PK model estimates for the allometric exponents were 0.77 for CL (and Q) and 0.87 for Vc (and Vp) (Table 4). Thus, the power functions describing each of these allometric relationships predicted that each parameter increased nonlinearly and in a less-than-proportional manner with increasing body weight. Given the magnitude and similar direction of these relationships on both the elimination and distribution parameters, these model-based results provided evidence of progressively reduced tedizolid exposures with increasing body size when the same dose was administered. After accounting for body weight, other covariates, including sex, age, race, total bilirubin, and eGFR, were found to not have a clinically relevant influence on tedizolid PK and exposures.

Table 4 - Parameter Estimates and Standard Errors for the Final Pediatric Population Pharmacokinetic Model for Tedizolid

Parameter		Final Parameter Estimate				Magnitude of Variability			
		Population Mean	%RSE	Bootstrap Mean[a]	Bootstrap 95% CI[a]	Final Estimate	%RSE	Bootstrap Mean[a]	Bootstrap 95% CI[a]
CL	Clearance (L/h) Body weight scale exponent (centered on 34 kg)[b]	3.71 0.770	3.02 4.85	3.71 0.773	3.50, 3.92 0.700, 0.848	33.9 %CV	18.1	33.0 %CV	27.6, 38.8 %CV
V_c	Central volume of distribution (L) Body weight scale exponent (centered on 34 kg)[c]	27.7 0.870	4.63 3.77	27.6 0.873	25.1, 30.0 0.811, 0.937	25.7 %CV	30.3	25.2 %CV	15.7, 31.9 %CV
Q	Intercompartmental clearance (L/h)	1.11	28.9	1.20	0.652, 2.03	NE	NA	NE	NE
V_p	Peripheral volume of distribution (L)	9.58	12.5	9.60	7.42, 11.80	NE	NA	NE	NE
SUSPF1	Bioavailability for oral suspension	0.854	6.34	0.860	0.760, 0.978	NE	NA	NE	NE
TABF1	Bioavailability for tablet	0.955	6.04	0.957	0.848, 1.07	NE	NA	NE	NE
D1	Duration for zero-order input for tablet (h)	1.90	22.7	1.90	0.438, 3.65	110 %CV	37.2	111 %CV	24.0, 216 %CV
k_a	First-order absorption rate constant (1/h)	0.620	15.7	0.654	0.404, 1.04	121 %CV	30.3	96 %CV	56.3, 137 %CV
RV for Phase 1 IV data (log scale)		0.0688	38.9	0.0669	0.0262, 0.130	0.262 SD	NA	0.259 SD	0.162, 0.360 SD
RV for Phase 1 Oral and Phase 3 data (log units)		0.282	13.2	0.280	0.214, 0.352	0.531 SD	NA	0.529 SD	0.463, 0.594 SD
Minimum Value of the Objective Function = -148.004									

Abbreviations: CI, confidence interval; %CV, coefficient of variation expressed as a percent; IIV, interindividual variability; IV, intravenous; NA, not applicable; NE, not estimated; %RSE, relative standard error expressed as a percent; RV, residual variability; SD, standard deviation.

[a] Mean and 95% CI values were obtained from bootstrap calculations (935 successful runs out of a total of 1000).

[b] Value of body weight scale exponent also applied to Q.

[c] Value of body weight scale exponent also applied to V_p.

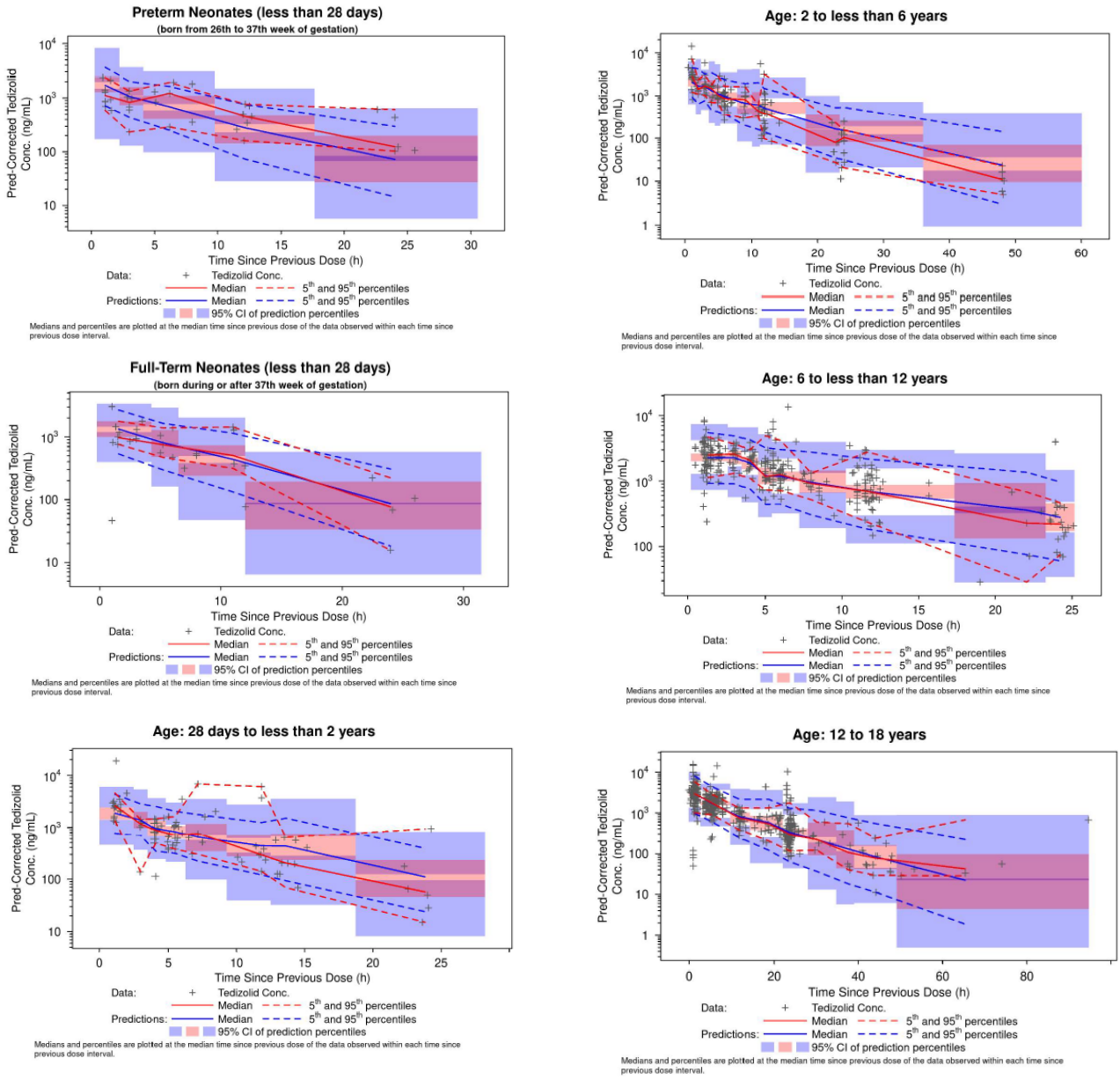
Note: Shrinkage estimates: 15.7% for IIV in CL, 47.2% for IIV in V_c, 65.4% for IIV in D1, and 50.3% for IIV in k_a.

KIWI Run 383652.

Numerical and graphical diagnostics, including precision of parameter estimates, goodness-of-fit plots, and pcVPC supported that individual model-predicted measures of tedizolid exposures were useful for the assessment of E-R relationships for related efficacy, safety, and target attainment analyses. Further, the results of the pcVPC and bootstrap assessments provided further confirmation that the final paediatric population PK model adequately described the observed tedizolid concentration data to be used for predictive purposes. Model evaluation using simulation-based visual predictive checks stratified

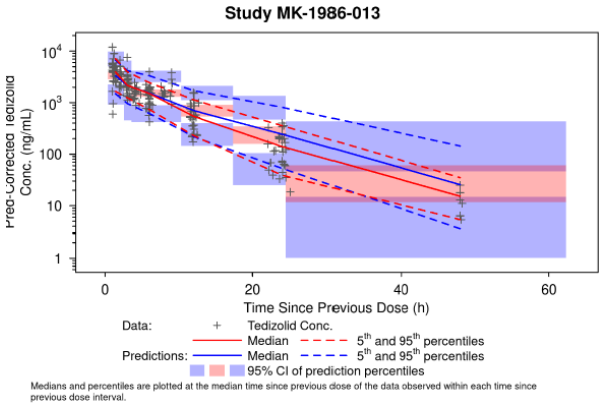
by the different age groups (Figure 2) showed that the model accurately characterized the central tendency of the observed data and that an appropriate distribution of the observed data fell with the 5th and 95th percentiles of model-simulated data, indicating that the model adequately describes the tedizolid concentration data across the age continuum for paediatric participants aged birth to <18 years of age.

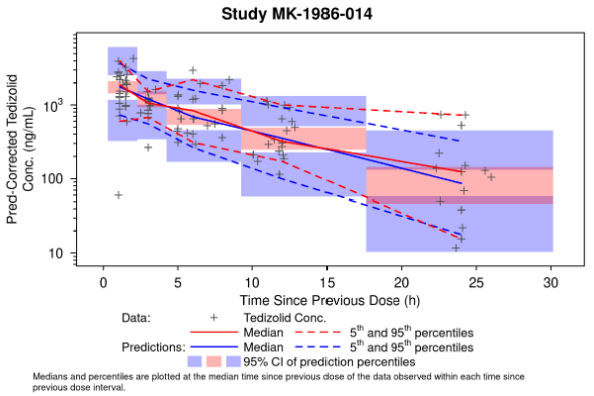
Figure 2 - Visual Predictive Check for Tedizolid by Age Group of Pediatric Population



Same plots are presented by study (Figure 3), weight band (Figure 4) and also for multiple-dose administrations (Figure 5).

Figure 3 - Prediction-Corrected Visual Predictive Check of the Final Tedizolid Population Pharmacokinetic Model, Stratified by Study





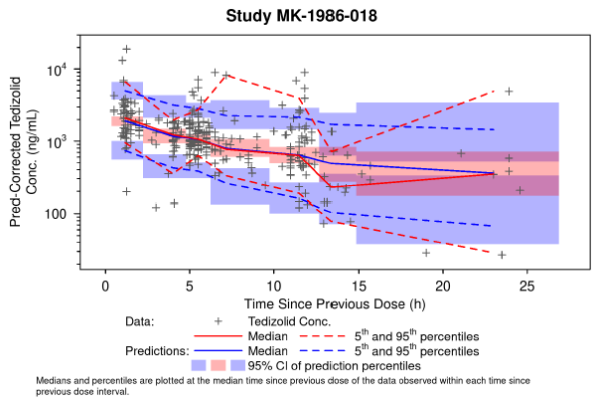
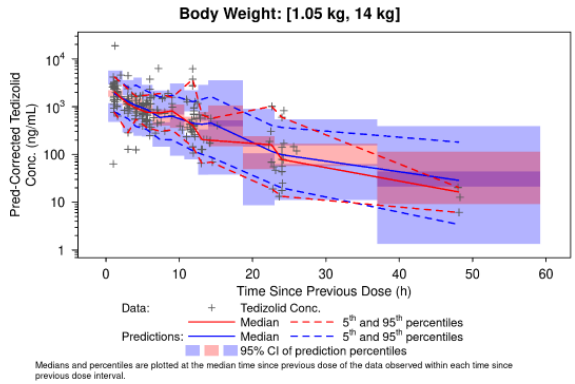
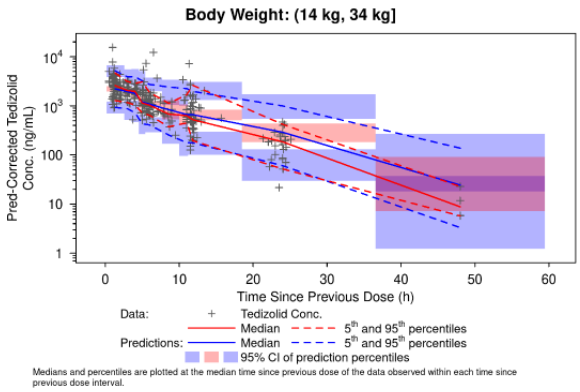
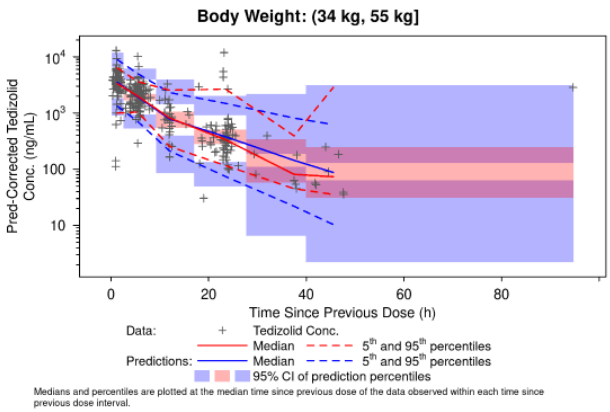


Figure 4 - Prediction-Corrected Visual Predictive Check of the Final Tedizolid Population Pharmacokinetic Model, Stratified by Quartiles of Body Weight







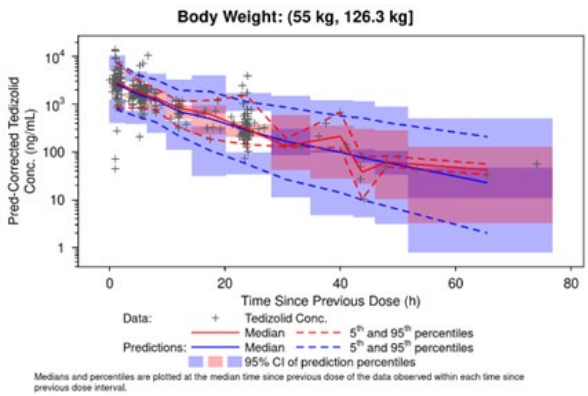
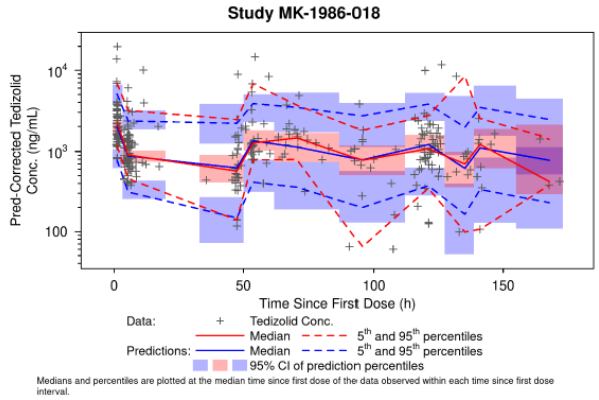


Figure 5 - Prediction-Corrected Visual Predictive Check of the Final Tedizolid Population Pharmacokinetic Model for the Multiple-Dose Studies, Plotted Versus Time Since First Dose



The goodness-of-fit plots for the final population PK model (*Figure 6*) indicated that the final model, including estimated allometric body weight scaling, provided an adequate characterization of single-dose and multiple-dose tedizolid PK following both IV and oral administration of tedizolid phosphate. Further, the model performed well in predicting PK across the full range of age categories and body weight quartiles.

To confirm that the final paediatric population PK model adequately characterized tedizolid PK in the adolescent population and could sufficiently predict exposures in adolescent patients 12 to < 18 years of age, an external validation was performed to compare model-predicted exposures between the paediatric and adolescent population PK models (Table 5). Additionally, a comparison of model-predicted versus tedizolid exposures based upon the NCA was done following a single dose of tedizolid phosphate in paediatric patients from P013 and P014 with dense PK sampling, stratified by age group, route of administration, and dose (Table 6).

Taken together, the validation results support the fidelity of the paediatric population PK model over the entire age range (birth to < 18 years) following IV and oral administration and support the application of the model to explore alternative dose regimens using simulation-based approaches.

Stochastic simulations (including the contribution of random IIV in PK parameters) using the final population PK model and a virtual population of paediatric patients with a uniform distribution of body weights ranging from 1 kg to 50 kg, irrespective of age, were performed to generate and compare tedizolid exposures to support the proposed weight banded dosing. The PTA was evaluated in a virtual paediatric population <18 years of age derived from the NHANES database and for participants enrolled in P018. Using the final population PK model, tedizolid plasma concentration profiles were simulated by Monte Carlo simulation in a total of 4000 virtual participants randomly sampled from the NHANES database with 1000 participants for each paediatric age group (12 to <18 years of age, 6 to <12 years of age, 2 to <6 years of age, and birth to <2 years of age). Additionally, post hoc estimates of individual PK parameters for the participants enrolled in the paediatric trials (P012, P026, P013, P014, and P018) were obtained from the final population PK model based on the actual dosing histories and individual covariates.

Figure 6 - Goodness of Fit Plots for Population PK Model for Tedizolid in Pediatric Participants <18 Years of Age

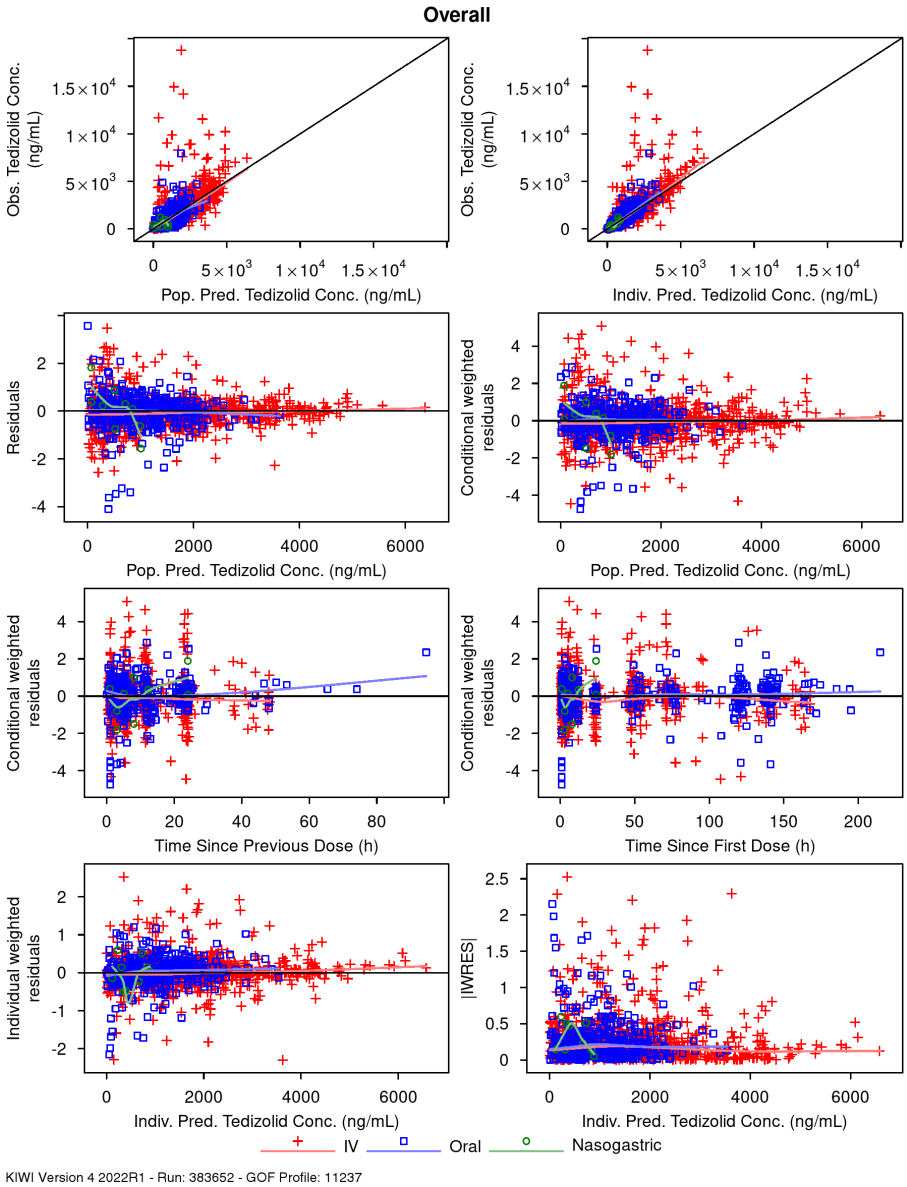


Table 5 - Comparison between the Adolescent and the Pediatric Population PK Model-Predicted PK Parameter Values for Tedizolid in Adolescent Participants in P012 Receiving IV or Oral Dosing of 200-mg Tedizolid Phosphate Once Daily for 6 Days

Population	N	Population PK Model	$AUC_{0\text{-}24h\_day\ 1}$ (µg·h/mL) GM (95% CI)	$AUC_{0\text{-}24h\_last}$ (µg·h/mL) GM (95% CI)	$C_{max\_day\ 1}$ (µg/mL) GM (95% CI)	C_{max_last} (µg/mL) GM (95% CI)
Adolescent (P012)	91	Adolescent Model	26.6 (24.9, 28.4)	28.6 (26.6, 30.8)	2.61 (2.27, 3.01)	3.13 (2.89, 3.38)
		Pediatric Model	26.1 (25.5, 28.3)	29.8 (29.0, 33.1)	3.33 (3.27, 3.69)	3.05 (3.00, 3.44)

$AUC_{0\text{-}24h\_last}$=Area under the concentration-time curve from 0 to 24 hour after the last dose; $AUC_{0\text{-}24h\_day\ 1}$=Area under the concentration-time curve from 0 to 24 hour after the first dose; CI=confidence interval; C_{max_last}=maximum concentration after the last dose; $C_{max\_day\ 1}$=maximum concentration after the first dose; GM=Geometric mean; IV=intravenous; PK=pharmacokinetics.

Table 6 - Model Predicted Versus NCA Summary Statistics of the PK Parameters for Tedizolid After Receiving a Single Dose of Tedizolid Phosphate in Pediatric Participants (Birth to <12 years) in P013 and P014

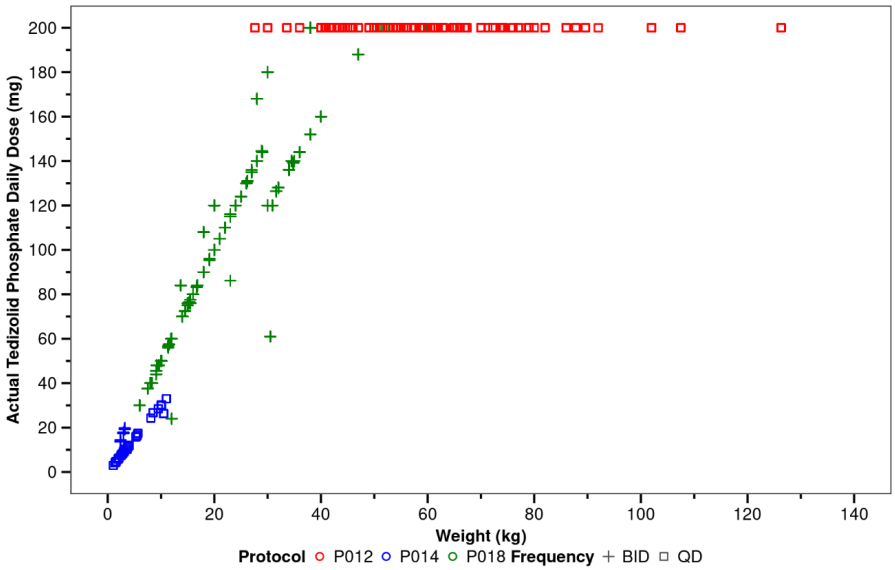
Study	Age Group	Route	Dose (mg/kg)	Statistic	Parameters based on NCA			Model-Predicted Parameters		
					$AUC_{0\text{-}inf}$ (µg × h/mL)	C_{max} (µg/mL)	T_{max} (h)	$AUC_{0\text{-}inf}$ (µg × h/mL)	C_{max} (µg/mL)	T_{max} (h)
P013	6 to < 12 years	IV	5	N	5	5	5	5	5	5
				GM (% GCV)	29.6 (27.8)	4.96 (17.0)	1.22 (12.7)	30.42 (26.43)	4.69 (6.31)	1.11 (6.45)
		IV	4	N	5	5	5	5	5	5
				GM (% GCV)	21.0 (45.2)	4.14 (39.5)	1.11 (11.9)	22.50 (40.59)	3.79 (24.31)	1.01 (9.44)
		Oral	4	N	6	6	6	6	6	6
				GM (% GCV)	24.9 (12.6)	2.59 (44.4)	2.66 (61.6)	24.52 (10.71)	1.99 (28.24)	3.10 (51.92)
	2 to < 6 years	IV	6	N	5	5	5	5	5	5
				GM (% GCV)	27.3 (26.4)	7.46 (22.5)	1.12 (3.6)	26.47 (26.13)	5.93 (7.25)	1.02 (4.26)
		IV	3	N	5	5	5	5	5	5
				GM (% GCV)	17.3 (24.5)	4.19 (47.7)	1.02 (2.3)	16.19 (21.68)	3.06 (19.32)	1.00 (0.74)
		Oral	3	N	6	6	6	6	6	6
				GM (% GCV)	17.2 (39.5)	1.82 (58.9)	4.00 (59.4)	15.11 (14.35)	1.37 (22.78)	2.84 (28.45)
P014	28 days to < 2 years	IV	3	N	10	10	10	8	8	8
				GM (% GCV)	14.3 (40.4)	2.19 (51.0)	1.29 (19.1)	13.09 (28.91)	2.37 (18.81)	1.01 (2.28)
	Full-term neonates	IV	3	N	5	6	6	5	6	6
				GM (% GCV)	9.21 (128)	0.962 (71.9)	1.41 (33.4)	13.14 (49.23)	1.72 (13.27)	1.04 (9.13)
	Pre-term neonates	IV	3	N	3	5	5	6	8	8
				GM (% GCV)	17.8 (20.9)	1.35 (44.5)	2.03 (90.0)	12.97 (34.14)	1.59 (23.01)	0.98 (7.22)

$AUC_{0\text{-}inf}$, area under the concentration-time curve from 0 to infinity; C_{max}, maximum plasma concentration; GCV, geometric coefficient of variation; GM, geometric mean; IV, intravenous; N, number of subjects; NCA, non-compartmental analysis; T_{max}, time of maximum concentration.

Analyses Supporting Proposed Dosage Recommendations

The previously submitted supplemental application supported the use of 200-mg tedizolid phosphate (IV or oral) once daily in adolescents 12 years to <18 years of age without regard to weight. For participants <12 years of age, weight-based dosing was utilized in the paediatric clinical trials. Initially, to explore the feasibility of weight-adjusted approaches across the paediatric population (birth to <18 years), the accrued clinical data for participants receiving multiple doses of tedizolid phosphate in P012, P014, and P018 were analyzed (Figure 7). Participants weighing ≥ 50 kg consistently received 200 mg once daily tedizolid phosphate (P012 and P018) and participants <25 kg consistently received twice daily, weight-based dosing of tedizolid phosphate (P014 and P018). In the weight range 25 to <50 kg, participants either received once daily, fixed doses of tedizolid phosphate (≥ 12 years in P012) or twice daily, weight-based doses of tedizolid phosphate (<12 years in P018) and this difference required further analysis and reconciliation to evaluate weight-banded dosing.

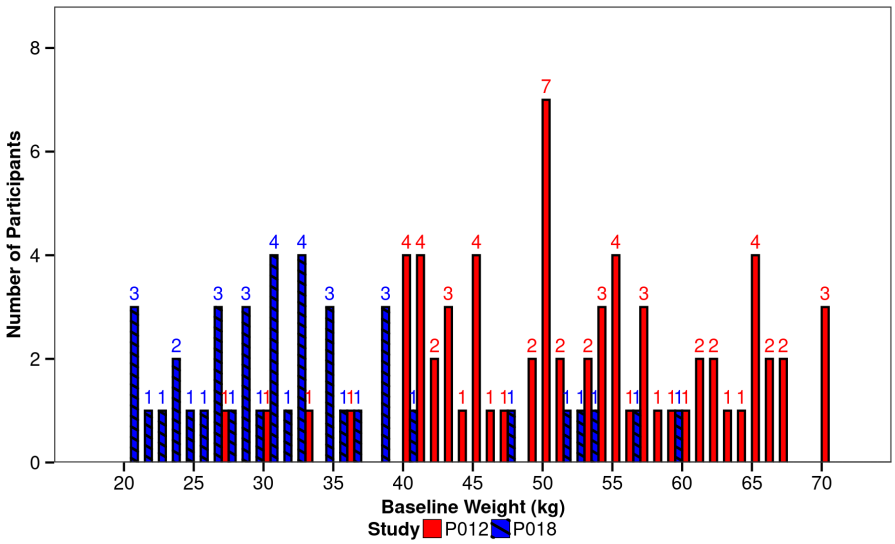
Figure 7 - Total Daily Dose Administered to Participants Receiving Multiple Doses of Tedizolid Phosphate in P014, P018 and P012



A complimentary analysis was conducted in this weight range of 25 to <50 kg with a focus on investigating the weight threshold wherein once daily dosing could transition to twice daily dosing of tedizolid phosphate. (Figure 8) shows the distribution of body weight for the participants in P012 and P018 and

Table *7* details the number of participants receiving the different dosage of tedizolid phosphate (IV or oral dosing) in 3 different weight ranges (25 to <35 kg, 35 to <50 kg and ≥50kg).

Figure 8 - Distribution of Body Weight in Participants (Weight Range = 20 kg to 70 kg) Receiving Multiple Doses of Tedizolid Phosphate in P012 and P018



The number above each bar represents the number of participants in each bar.

Table 7- Clinical Doses and Number of Participants in the Weight Range of ≥25 kg in P018 and P012 who Received Multiple Doses of Tedizolid Phosphate as an IV infusion or as an Oral Formulation

Protocol	Weight Band	Clinical Dosage	Total Daily Dose (mg)	N
P018	≥50 kg	200 mg/Once daily	200	5
	35 to <50 kg	2 mg/kg/Twice daily	140 to less than 200	7
	25 to <35	2.5 mg/kg/Twice daily	125 to less than 175	21
P012	≥50 kg	200 mg/Once daily	200	65
	35 to <50 kg			23
	25 to <35			3
N=number of participants.				

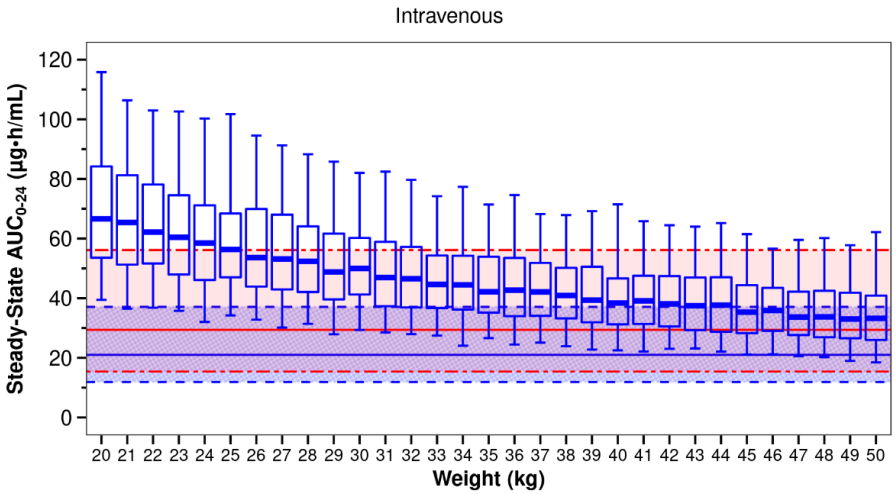
In P012, most of the participants (88 of 91) weighed ≥35 kg with only 3 participants weighing <35 kg receiving 200 mg once daily tedizolid phosphate. A majority of participants (23 of 30) in the weight range of 35 to <50 kg in P012 and P018 received once daily tedizolid phosphate for ≥6 days providing confidence in the use of 200 mg once daily tedizolid phosphate in participants ≥35 kg adequately supported by clinical efficacy and safety experience. By comparison, most (21 of 24) of the clinical experience in participants 25 to <35 kg) was based upon P018, following twice daily weight-based dosing. Therefore, a potential threshold of 35 kg was supported as the basis of a switch from once daily dosing (for participants ≥35 kg) to twice daily dosing (for participants <35 kg) of tedizolid phosphate. Of note, 1.5% of adolescents (≥12 years of age) weigh less than 35 kg in the NHANES database and therefore the refinement of the existing adolescent dosage recommendation based upon the threshold of 35 kg is expected to continue to be generally consistent with that previously approved.

To reconcile the clinical experience and the proposed dosage recommendation, simulations were performed in individual weight bins (kg increment) of 20 to 50 kg to support a switch from once daily to twice daily dosing of tedizolid phosphate in the paediatric population.

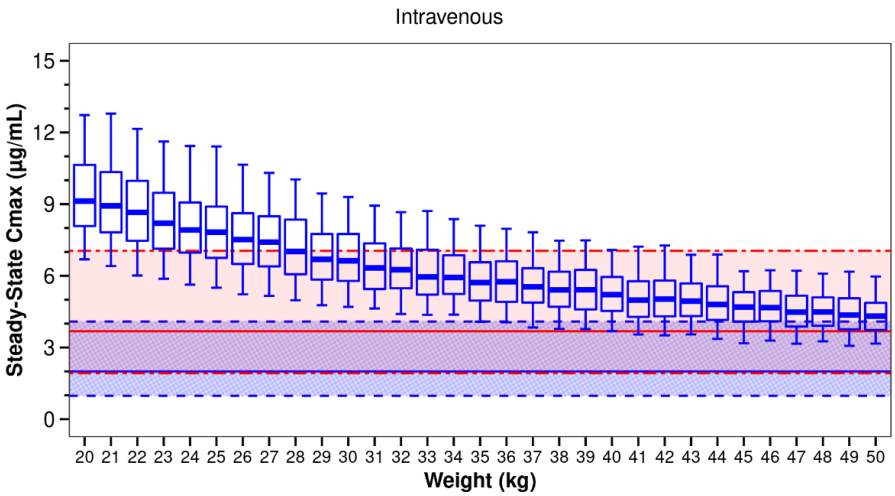
Steady-state PK profiles were simulated for the virtual population receiving a once daily IV infusion or an oral tablet of 200-mg tedizolid phosphate in the weight range of 20 to 50 kg.

Figure 9 and Figure 10 illustrate the steady-state AUC and Cmax of tedizolid after administration of once daily 200-mg tedizolid phosphate as an IV infusion or as an oral tablet, respectively, stratified by weight bins (kg increment) ranging from 20 to 50 kg compared to the adult and adolescent reference exposures. Following dosing of either IV or oral tablet of tedizolid phosphate, greater excursions from the adult and the adolescent AUC and Cmax would be expected at lower weights.

Figure 9 - Steady State AUC0-24 (top panel) and Cmax (bottom panel) From Simulated Exposures for the Virtual Population receiving Once Daily 200-mg Tedizolid Phosphate as an IV Infusion Stratified by Weight Bins Ranging From 20 kg to 50 kg.



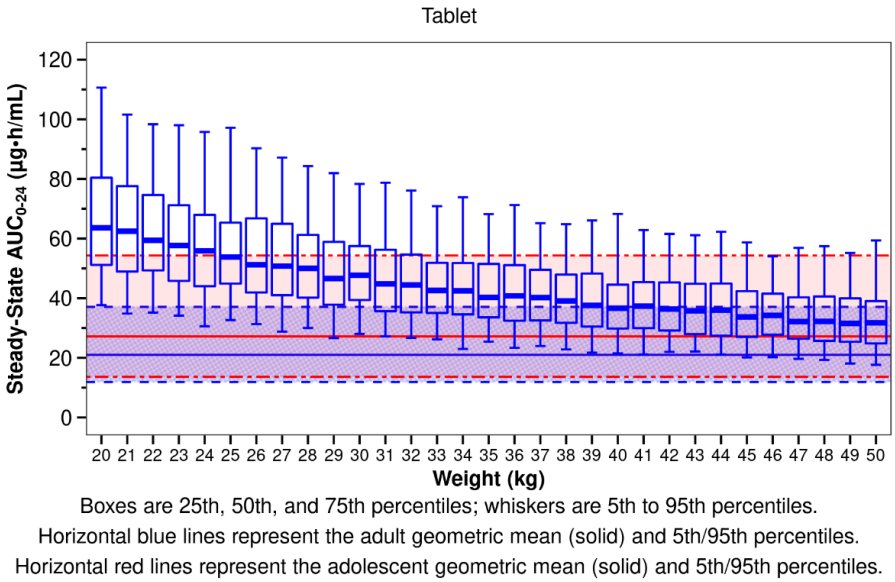
Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Horizontal blue lines represent the adult geometric mean (solid) and 5th/95th percentiles.
Horizontal red lines represent the adolescent geometric mean (solid) and 5th/95th percentiles.

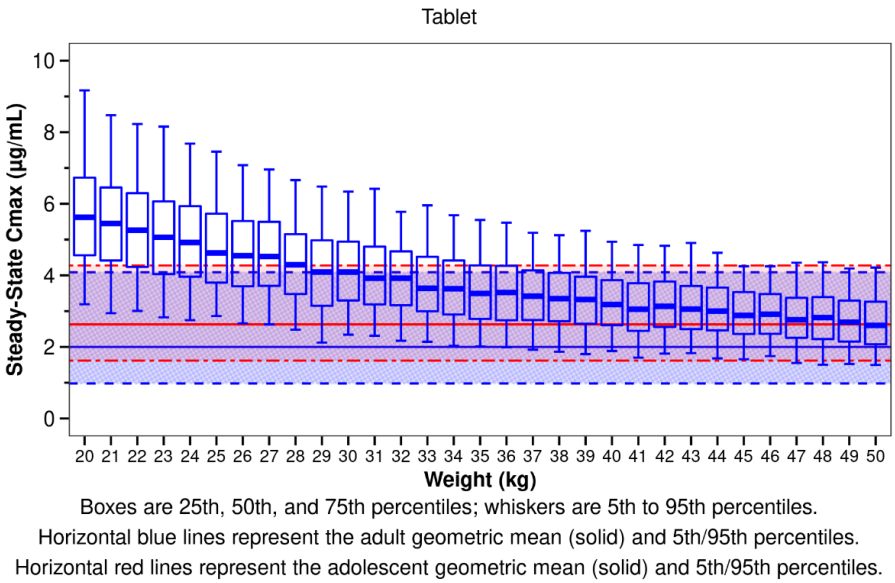


Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Horizontal blue lines represent the adult geometric mean (solid) and 5th/95th percentiles.
Horizontal red lines represent the adolescent geometric mean (solid) and 5th/95th percentiles.

AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; C_{max}, maximum plasma concentration.

Figure 10 - Steady State AUC0-24 (top panel) and Cmax (bottom panel) From Simulated Exposures for the Virtual Population Receiving Once Daily 200-mg Tedizolid Phosphate as an Oral Tablet Stratified by Weight Bins Ranging From 20 kg to 50 kg





AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; C_{max}, maximum plasma concentration.

Specifically, for patients weighing <35 kg there would be a greater tendency for the interquartile range of tedizolid AUC and Cmax to exceed the 95th percentile of the adolescent clinical experience. Although there has been no evidence of a safety concern related to upper limit of exposures (AUC and Cmax), paediatric dosing based upon comparability to the adult PK experience was applied and supports extrapolation of efficacy and safety bridging. To minimize any safety concerns in the lower weight paediatric population (<35 kg), regardless of age, twice daily dosing of tedizolid phosphate is expected to result in minimal excursions in Cmax while maintaining similar AUC when tedizolid phosphate would be dosed based on the body weight of the patient. For patients who weigh ≥35 kg, the tedizolid exposure may be higher than the experience in adults but would be generally similar to the experience in

adolescent patients for IV or oral dosing of tedizolid phosphate. In the adult program, safety was established up to 1200-mg tedizolid phosphate (details presented in the previous submission) wherein the geometric mean Cmax was reported as 9.49 µg/mL and 10.77 µg/mL in 2 separate Phase 1 studies, providing further support for the use of 200 mg tedizolid phosphate once daily (either as an IV infusion or as an oral tablet) for patients weighing ≥35 kg.

As such, in order to support the proposed recommended dosing regimens for patients weighing <35 kg, steady-state PK profiles were simulated for participants receiving tedizolid phosphate either twice daily (IV infusion for participants <35 kg) or once daily (IV infusion or oral tablet for participants ≥35 kg) based on the proposed recommended weight-banded dosage (Table 8) to: (1) confirm the appropriateness of transition from once-daily to twice daily tedizolid phosphate and, (2) to determine exposures (AUC and Cmax) supporting the weight-banding approach for the proposed dosage recommendations. For comparison to adults, simulated steady state AUC and Cmax in adults receiving 200-mg tedizolid phosphate (either as an IV infusion or as an oral tablet) were utilized.

Table 8 - Proposed Oral and IV Dosage of Tedizolid Phosphate Based on the Body Weight

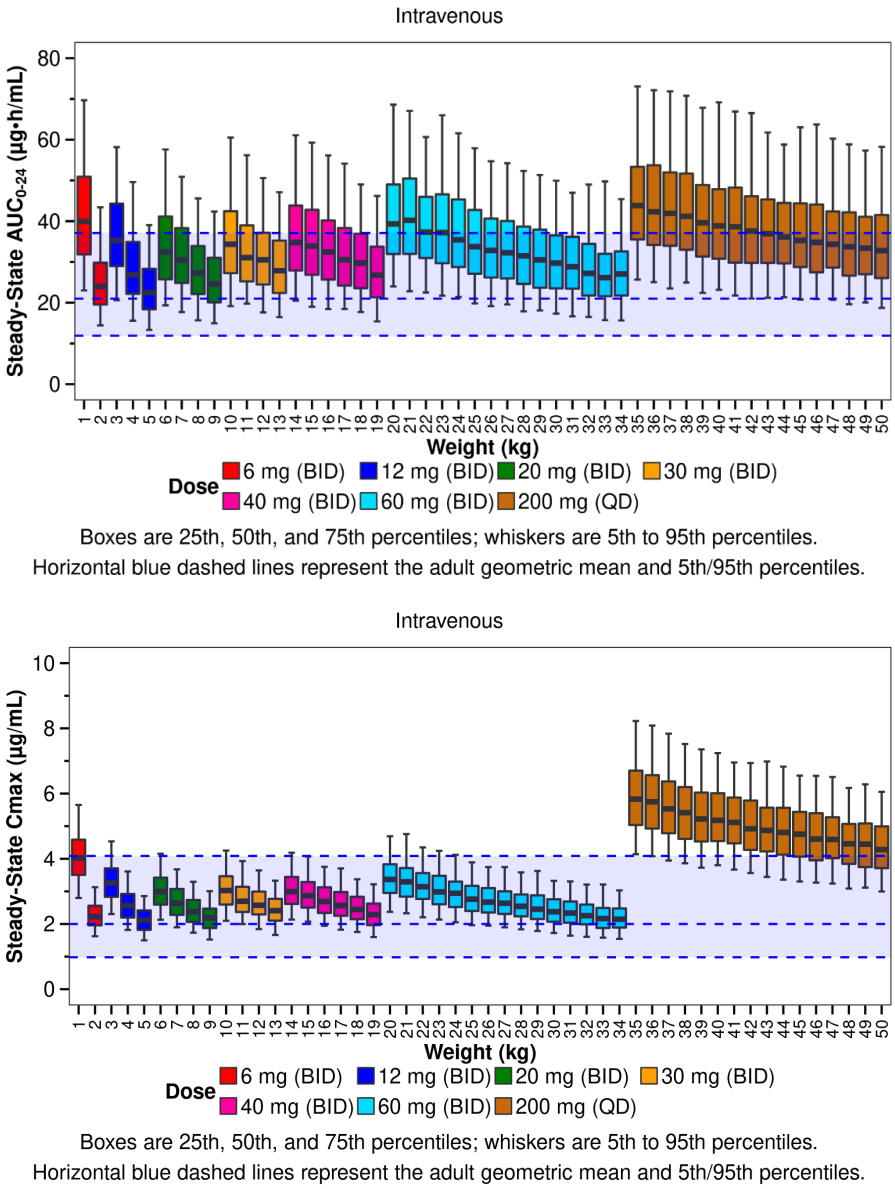
Route	Weight Band (kg)	Dosage	Frequency
IV	1 to less than 3	6 mg	Twice daily
	3 to less than 6	12 mg	Twice daily
	6 to less than 10	20 mg	Twice daily
	10 to less than 14	30 mg	Twice daily
	14 to less than 20	40 mg	Twice daily
	20 to less than 35	60 mg	Twice daily
	≥35	200 mg	Once daily
Oral[a]	≥35	200 mg	Once daily

IV=intravenous.

[a] Oral tablet formulation

Figure 11 shows steady-state AUC and Cmax exposures at the recommended dosage regimen of tedizolid phosphate stratified in different weight bins for participants receiving multiple IV infusions of tedizolid phosphate. Steady-state AUC is expected to be marginally higher than the adult experience but generally similar to the adolescent experience (see Figure 9 and Figure 10) providing confidence in the extrapolation of efficacy in paediatric population. The utilization of twice daily dosing for patients weighing <35 kg is largely expected to result in Cmax within the adult experience. As discussed previously, the AUC and Cmax for participants weighing ≥35 kg, especially those in the range of 35 to 50 kg, are largely expected to be within the clinical experience in adolescents while exceeding the adult experience at the once daily dose of 200-mg tedizolid phosphate (see Figure 9 and Figure 10) and are not considered clinically significant. In any case, exposure in the 1 kg body weight cohort seems to exceed that of the adult reference. Additionally, the pcVPC for the preterm neonate cohort indicates an underprediction of tedizolid PK, raising our concern of potentially even higher exposure.

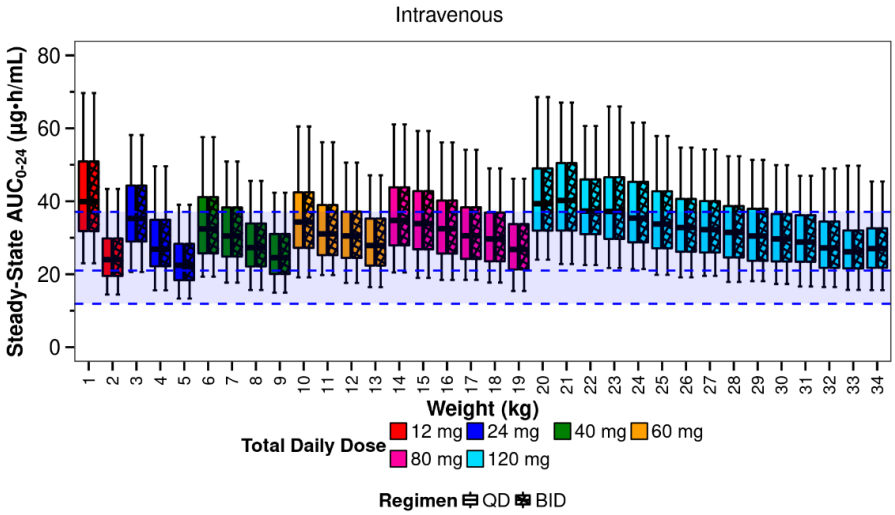
Figure 11 - Distribution of Model-Predicted Tedizolid Steady State AUC0-24 (top panel) and Cmax (bottom panel) by Weight Bins After multiple IV infusions of Tedizolid Phosphate in Virtual Pediatric Subjects



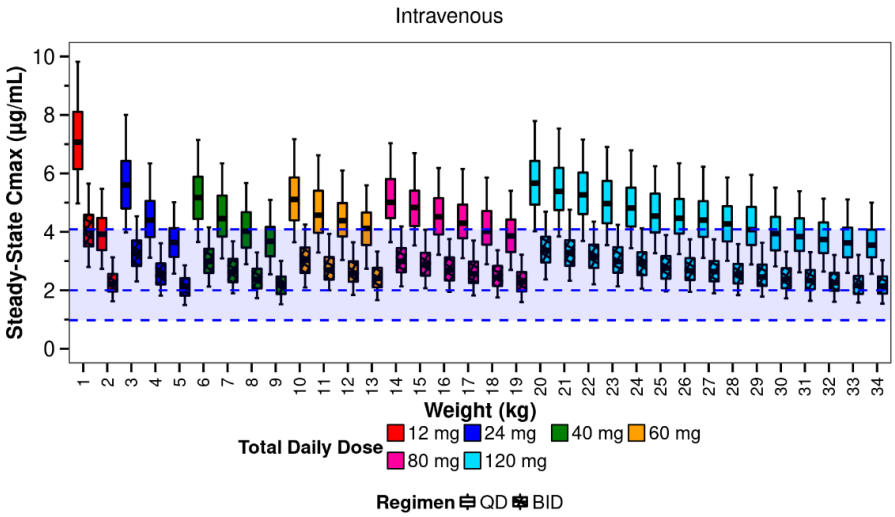
AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; BID, twice daily; C_{max}, maximum plasma concentration; QD, once daily.

To compare the impact of dosing regimen (once daily and twice daily), simulations were conducted in which the total daily dose was based on the proposed weight-banded strategy, but with the dose for each weight band administered either once daily or twice daily to achieve the same total daily dose (Figure 12) for patients weighing<35 kg. As expected, a twice daily regimen considerably reduces the excursions in steady-state C_{max} with concentrations of tedizolid expected to be within the 5th to 95th percentiles of the adult patient experience across the full range of body weights explored. By comparison and as expected, steady-state AUC0 24 is similar between once daily and twice daily dosing. Taken together, these results support twice daily administration of tedizolid phosphate, particularly for patients weighing <35 kg, to minimize excursions in C_{max}, while maintaining similar overall daily exposures compared to once daily.

Figure 12 - Distribution of Simulated Tedizolid Steady-State AUC0 24 and Cmax by Weight Bins After Multiple Intravenous Infusions of Tedizolid Phosphate in Virtual Pediatric Patients When Administered Once Daily or Twice Daily to Achieve the Same Total Daily Dose



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



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

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

As a measure of fidelity between the weight-banded approach and the clinical trial experience, exposures from the recommended dosage regimen of tedizolid phosphate based on the weight bands were compared to the empirical Bayesian estimates of exposures for the weight-based dosing of tedizolid phosphate in P018 and P012 based on the actual dosing history of the participants. The pronounced similarity between the exposures at the doses evaluated in the clinic and those projected at the proposed weight-banded doses indicates that the safety experience in the clinical studies for paediatric participants may be extended to patients receiving weight-banded dosing. The steady state exposures within each weight band for the PK analysis population (P012, P013, P014, P018, P026) birth to <18 years of age and for the population in the clinical trials for participants <12 years of age (P013, P014 and P018) are

summarized in Table 9. Compared to the adult patients receiving 200-mg tedizolid phosphate once daily, the predicted AUC and Cmax are generally higher though the higher exposures are not considered clinically significant.

Table 9 - Predicted Steady State Exposures (AUC0-24 and Cmax) Following Multiple Dose Administration of Intravenous or Oral Tedizolid Phosphate Based Upon the Proposed Weight-Banded Dose Regimen for Tedizolid Phosphate in Pediatric Participants (Birth to <18 Years) From the Pharmacokinetic Analysis Population

Body Weight (kg)	**Dosage**	**Frequency**	**Route**	**N**	**Steady State AUC_{0-24} (µg × h/mL) GM (%CV)[b]**	**Steady State C_{max} (µg/mL) GM (%CV)**
1 to < 3	6 mg	Twice daily	IV	14	28.41 (48.25)	2.22 (34.36)
3 to < 6	12 mg	Twice daily	IV	13	26.40 (34.38)	2.40 (20.71)
6 to < 10	20 mg	Twice daily	IV	13	22.54 (43.87)	2.22 (20.37)
10 to < 14	30 mg	Twice daily	IV	17	27.61 (32.14)	2.68 (19.57)
14 to < 20	40 mg	Twice daily	IV	25	28.44 (22.09)	2.74 (12.95)
20 to < 35	60 mg	Twice daily	IV	45	31.40 (29.94)	2.61 (21.63)
≥ 35	200 mg	Once daily	IV	122	30.63 (29.68)	3.83 (23.90)
		Once daily	Oral[a]	122	29.25 (29.67)	2.50 (24.42)

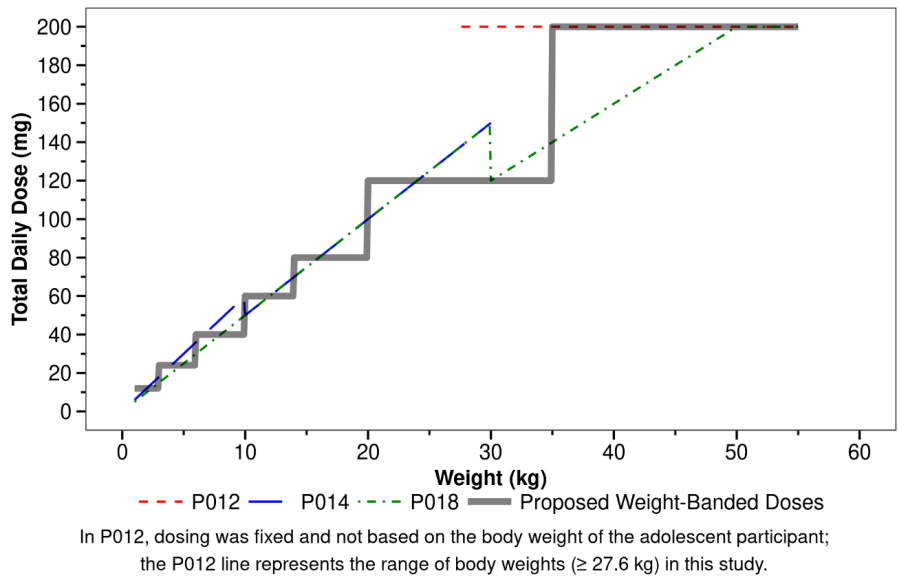
AUC_{0-12h}, area under the concentration-time curve from 0 to 12 hours; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; C_{max}, maximum plasma concentration; %CV, coefficient of variation expressed as a percent; GM, geometric mean; IV, intravenous.

[a] Oral tablet formulation

[b] $AUC_{0-24} = 2 \times AUC_{0-12}$ for twice-daily dosing

In summary, the proposed paediatric dosing regimen results in no clinically relevant differences in the disposition of tedizolid between paediatric and adult populations, with tedizolid exposures in paediatric patients broadly contained within those observed in adults, whereby efficacy and safety have been previously established. Rather than weight-based dosing based precisely on patient weight, a weight-banded dosing is proposed. In this regard, although the regimen of fixed doses is proposed for defined weight ranges, the basis for the doses is predicated upon the weight-based regimens evaluated in P014 and P018 (Figure 13). The proposed weight-banded dosage is also supported by the PTA analysis indicating expected effectiveness in paediatric patients.

Figure 13 - Comparison of the Recommended Weight-Banded Tedizolid Phosphate Total Daily Dose and the Weight Based Tedizolid Phosphate Daily Dose Administered in P012, P014, and P018



2.3.3. Pharmacodynamics

Mechanism of action

Tedizolid phosphate is an oxazolidinone phosphate prodrug. The antibacterial activity of tedizolid is mediated by binding to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis. Tedizolid is primarily active against Gram-positive bacteria. Tedizolid is bacteriostatic against enterococci, staphylococci, and streptococci in vitro.

The most commonly observed mutations in staphylococci and enterococci that result in oxazolidinone resistance are in one or more copies of the 23S rRNA genes (G2576U and T2500A). Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to tedizolid. A second resistance mechanism is encoded by a plasmid-borne and transposon associated chloramphenicol-florfenicol resistance (cfr) gene, conferring resistance in staphylococci and enterococci to oxazolidinones, phenicols, lincosamides, pleuromutilins, streptogramin A and 16 membered macrolides. Due to a hydroxymethyl group in the C5 position, tedizolid retains activity against strains of *Staphylococcus aureus* that express the cfr gene in the absence of chromosomal mutations. The mechanism of action is different from that of non-oxazolidinone class antibacterial medicinal products; therefore, cross-resistance between tedizolid and other classes of antibacterial medicinal products is unlikely.

2.3.4. PK/PD modelling

Exposure Response for Efficacy

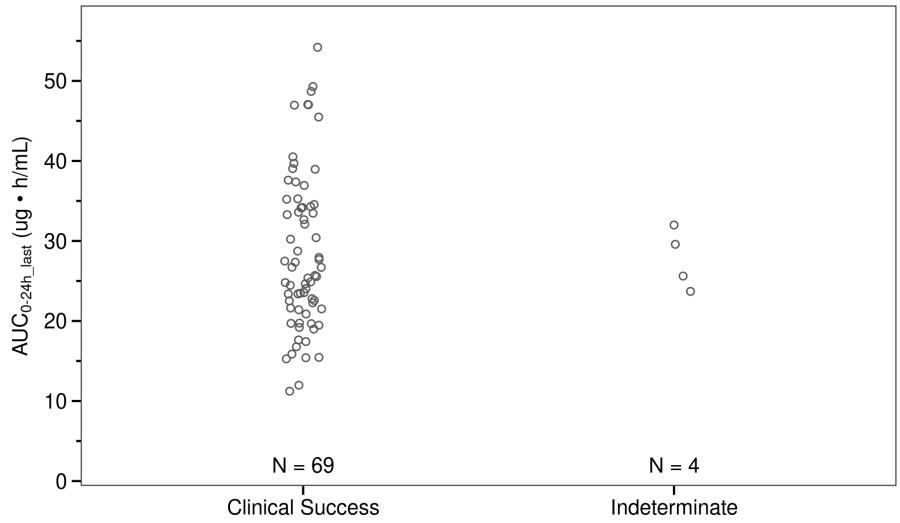
An efficacy exposure-response analysis was planned to investigate the relationship, if any, between tedizolid exposure and clinical response. The analysis was based on the data from 1 completed Phase 3 study P018 that evaluated efficacy and safety in participants <12 years of age with ABSSSI.

The population in the E-R efficacy data analyses included only those patients who had available tedizolid exposure measures (73 of 75) and/or available *Staphylococcus aureus* MIC values (35 of 75). Individual MIC values were obtained from isolates tested in the study. It should be noted that previous analyses of adult data and adolescent data showed no relationship between fAUC/MIC or AUC and efficacy outcome following dosing of 200 mg once daily tedizolid phosphate indicating that the tedizolid exposure at this dose were sufficient for efficacy. As such, no trend between fAUC/MIC or AUC and efficacy outcome was expected in paediatric patients in the efficacy/safety trials, and no formal modelling was planned.

In the absence of clinical failure for patients enrolled in P018 and who received tedizolid phosphate, no exposure response relationship would be identified, and this analysis was explored to assess any differences in the distribution of the PK exposures based upon graphical comparisons, specifically in the setting of indeterminate clinical outcomes. Clinical response at the test of cure (TOC; 25 days after the first infusion in P018) visit, in the ITT group was used for the analysis. AUC and fAUC/MIC were used as the tedizolid PK targets and were estimated based on the empirical Bayesian estimates from the population PK analysis following the last dose administered in each participant of P018 based on their actual clinical dose.

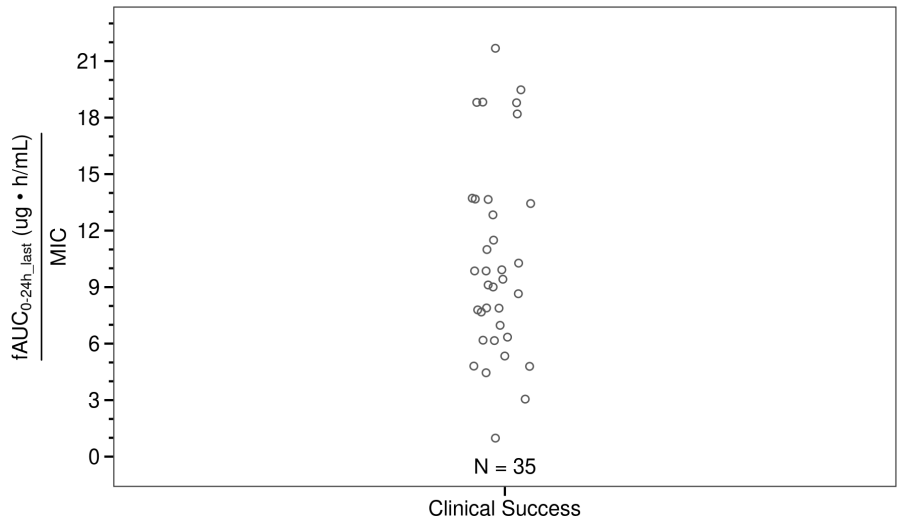
Graphical comparison of AUC for participants who achieved a clinical response (clinical success, ie, cure) versus participants with clinical response reported as indeterminate at the TOC visit indicated no visible trend in tedizolid AUC between these categories (Figure 14). Further, all participants for which the MIC value was available in P018 (N=35) had clinical success and represented a wide distribution of the fAUC/MIC (Figure 15).

Figure 14 - Distribution of Predicted Tedizolid AUC with Overall Response Between Cure and Indeterminate at ITT-TOC in P018



$AUC_{0\text{-}24,last}$, area under the concentration-time curve from time 0 to 24 hours after last dose; N, number of patients.

Figure 15 - Distribution of Tedizolid fAUC/MIC for the Clinical Success at ITT-TOC in P018



The number of subjects is below the set of points.

*f*AUC$_{0\text{-}24h_last}$, area under the concentration-time curve for free (unbound) drug concentration from time 0 to 24 hours after last dose; MIC, minimum inhibitory concentration; N, number of subjects.

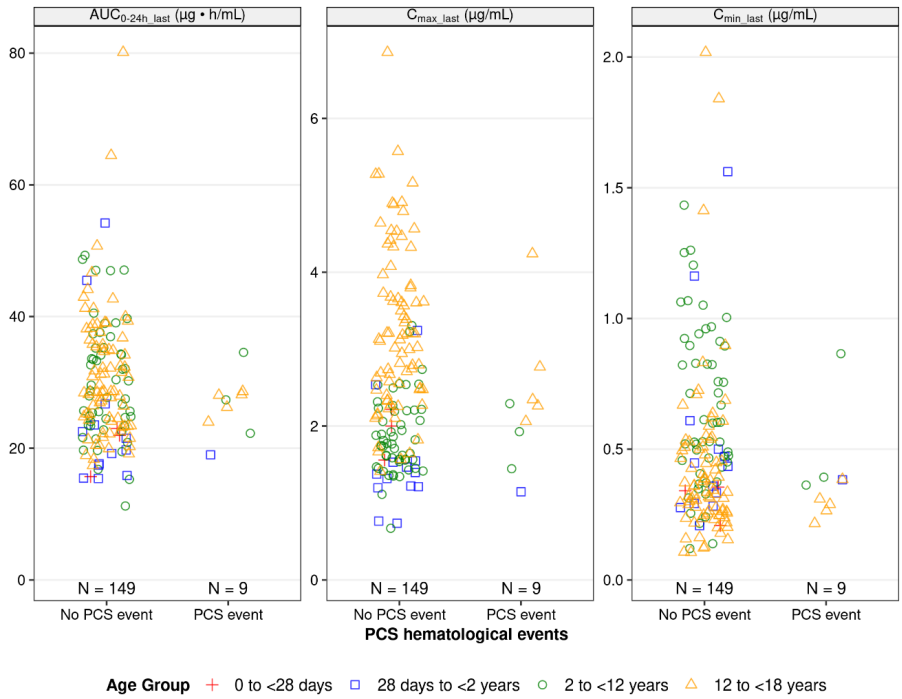
Exposure Response for Safety

To support the appropriateness of the clinical dosage of tedizolid phosphate administered orally or as an IV infusion over 1 hour in participants from birth to <18 years of age, a graphical exposure-safety assessment was conducted. The analysis focused on the incidence of substantially abnormal PCS haematological AEs from a total of 174 participants <18 years of age receiving multiple doses of tedizolid phosphate (in P012, P014 and P018).

Safety endpoints included post-baseline changes in haemoglobin, platelets, and neutrophils consistent with PCS hematologic low values. PCS haematologic low values are defined as values that are <75% of LLN (or <50% of LLN for absolute neutrophil count). AUC, C_{max}, and C_{min} exposure estimates were predicted following the last dose administered in each participant of the constituent studies (P012, P014, P018) based on post hoc estimates from the final population PK model and actual dosing histories for each participant.

PCS abnormal laboratory values (decreases in ANC, platelets, and haemoglobin) were explored for any potential association with tedizolid exposure for participants who received multiple doses of tedizolid phosphate (full-term and preterm neonates in P014, 28 days to <12 years in P018 and 12 to <18 years in P012). The distribution of exposures (AUC, C_{max}, and C_{min}) in participants aged birth to <18 years of age who experienced PCS abnormal laboratory values for decrease in ANC, platelets, and haemoglobin was comparable to that in participants who did not experience such changes (Figure 16). Over the range of tedizolid exposures estimated following multiple-dose administration of tedizolid phosphate in paediatric participants, no association between PK and the laboratory endpoints was observed.

Figure 16 - Distribution of Tedizolid Exposure in Participants (Pooled P012, P014, and P018) who experienced Versus Participants who did not Experience Potentially Significant Lowest Haematology Values After receiving Multiple Doses of Tedizolid Phosphate



$AUC_{0\text{-}24\_last}$, area under the concentration-time curve from time 0 to 24 hours after last dose; C_{max_last}, maximum plasma concentration after last dose; C_{min_last}, minimum plasma concentration after last dose; N, number of participants; PCS, potentially clinically significant.

2.3.5. Discussion on clinical pharmacology

The clinical studies were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such studies including the archiving of essential documents. All studies were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed. Their evaluation was already made in previous submissions and, at this time, only their PK/PD data was evaluated in a popPK model.

The tedizolid phosphate IV and tablet formulations referenced in this application are the same formulations as those approved for adults and adolescents; the composition and instructions for preparation and administration have been summarized in the prescribing information. Although a PFOS formulation in a multidose bottle presentation was developed and used to support the paediatric clinical studies (P013, P014, and P018), the current supplemental application is not intended to seek approval for the PFOS oral formulation. As such, no biopharmaceutics studies were conducted to support this supplemental application.

Pharmacokinetic evaluations for tedizolid were conducted in P013, P014, and P018. Tedizolid concentrations in P013, P014, and P018 were determined using a validated bioanalytical method, already assessed in the past. Tedizolid PK was evaluated using a population PK model derived from the 3 paediatric studies (P013, P014, and P018) and 2 additional clinical studies (MK-1986-012 (P012) and MK-1986-026 (P026)) in adolescents 12 to <18 years of age. The model integrated all available PK data in paediatric participants <18 years of age and included 1191 tedizolid plasma concentration records

from 249 participants. Of these, it should be reinforced that multiple dose data in neonates was poorly collected with 4 out of 7 subjects not being included in the study. However, taking in consideration that tedizolid shows linear and time-invariant kinetics, that there was a good characterization of the PK in single dose, the expected accumulation is not high and the available multiple-dose profiles do not show a significant departure from the expected behaviour, this lack of information at multiple doses does not seem to be problematic.

The update procedure was sufficiently explained and followed logical steps. The final model performed sufficiently well with minor changes in the overall parameters when compared to the original model, resulting in acceptable GOF and VPCs not showing significant deviations in all the different studies/class of populations. Also, the significance of the model parameters was confirmed by a bootstrap analysis. The shrinkage of some parameters was high. However, co-variate selection was made by forward and backward selection and is, thus, less dependent on this. Finally, Tedizolid exposures (AUC, C_{max}, and T_{max}) estimated from noncompartmental analysis and those estimated from model-based PK analysis were similar to those for adolescents and adults receiving 200 mg of tedizolid phosphate. Overall, the paediatric population PK model is considered acceptable and usable for the assessment of the influence of pertinent intrinsic factors (including age, body weight, IBW, race, renal function [eGFR], and liver function [total bilirubin]) on tedizolid PK, for the predicting of individual tedizolid exposures for use in PTA and E-R analyses and to perform stochastic simulations to comprehensively explore and critically evaluate potential dosing regimens.

Tedizolid PK in participants <12 years of age receiving IV infusion or oral dosing of tedizolid phosphate was characterized in P013, P014, and P018, with the primary objective of identifying a dosage regimen that achieves tedizolid exposures (AUC and Cmax) like those previously studied in adults. Weight-based dosing of tedizolid phosphate was utilized in these clinical trials, with participants weighing ≥50 kg receiving 200 mg once daily and participants <50 kg receiving a weight-based dose twice daily.

The empirical Bayesian estimates derived from the population PK model were used in the E R analysis. However, there were no clinical failures in P018 and any association between the PK of tedizolid and clinical success could not be ascertained. Similarly, graphical analysis of PCS abnormal laboratory values (decreases in ANC, platelets, and haemoglobin) was explored for any potential association with tedizolid exposure for participants receiving multiple doses of tedizolid phosphate in P014, P018, and P012, and no association between PK and the laboratory endpoints was observed.

The paediatric population PK model was used to support the proposed tedizolid phosphate dose recommendations in participants <12 years of age and refinement of the approved dosage of tedizolid phosphate in adolescents ≥12 years of age. These recommendations considered the totality of clinical and PK experience across the age (and weight) continuum of the paediatric population from birth to <18 years of age. Given that body weight is the only predictor of tedizolid PK in paediatric participants, dosage recommendations previously approved in the paediatric population ≥12 years of age were investigated for refinement and any reconciliation across the entire target paediatric population. The modification of the approved dosage for adolescents was intended to improve the comparability of exposure estimates across the paediatric population. Refinement of the dosage previously approved in adolescents was not related to any safety or efficacy concerns.

To support weight-banded dosing of tedizolid phosphate, a weight threshold was examined to switch from a tedizolid phosphate once-daily to twice-daily regimen. Based on analysis of a virtual population in the NHANES database and the clinical experience from participants receiving multiple doses of tedizolid phosphate, a threshold of 35 kg was selected as the basis to explore weight-banded approaches with the clinical and PK experience for those ≥35 kg largely informed by dosing of 200 mg once-daily tedizolid phosphate. Subsequently, for patients weighing <35 kg, incremental weight bands were investigated with twice-daily administration of tedizolid phosphate.

PK profiles were determined for the fixed doses of tedizolid phosphate IV infusion twice daily (for participants <35 kg) and IV infusion or oral tablet once daily (200 mg for participants ≥35 kg) for the paediatric participants in the population analysis dataset. Steady state AUC and C_{max} for tedizolid in paediatric participants were determined based on the different weight bands. The predicted AUC and C_{max} are generally similar across the different weight bands and to those in adults and thus, allow for the extrapolation of efficacy and safety bridging to those established in adults.

To simplify dosing in paediatric patients <18 of years of age, the Sponsor proposes weight banded dosing across the entire age range as follows:

Weight Band (kg)	Dosage	Frequency
1 to less than 3	6 mg	Twice daily
3 to less than 6	12 mg	Twice daily
6 to less than 10	20 mg	Twice daily
10 to less than 14	30 mg	Twice daily
14 to less than 20	40 mg	Twice daily
20 to less than 35	60 mg	Twice daily

Although the stochastically simulated steady-state tedizolid exposures of 6 mg BID for the 1 kg population shows that the 95th percentiles go above the adolescent 95th percentiles observed data, examination of individual predictions for neonatal participants in P014 indicates that exposures based upon the weight banded regimen are predicted to be within the adolescent experience, where effectiveness and safety were previously established.

2.3.6. Conclusions on clinical pharmacology

From a clinical pharmacology perspective, the proposed weight banded dosing of tedizolid phosphate IV infusion twice daily for participants <35 kg is acceptable. Administration of an IV infusion or oral tablet once daily of 200 mg) for the paediatric participants weighting ≥35 kg is also acceptable. The remaining additional data provided in part 5.2 of the SmPC is supported.

2.4. Clinical efficacy

2.4.1. Main study (MK-1986-018)

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

Methods

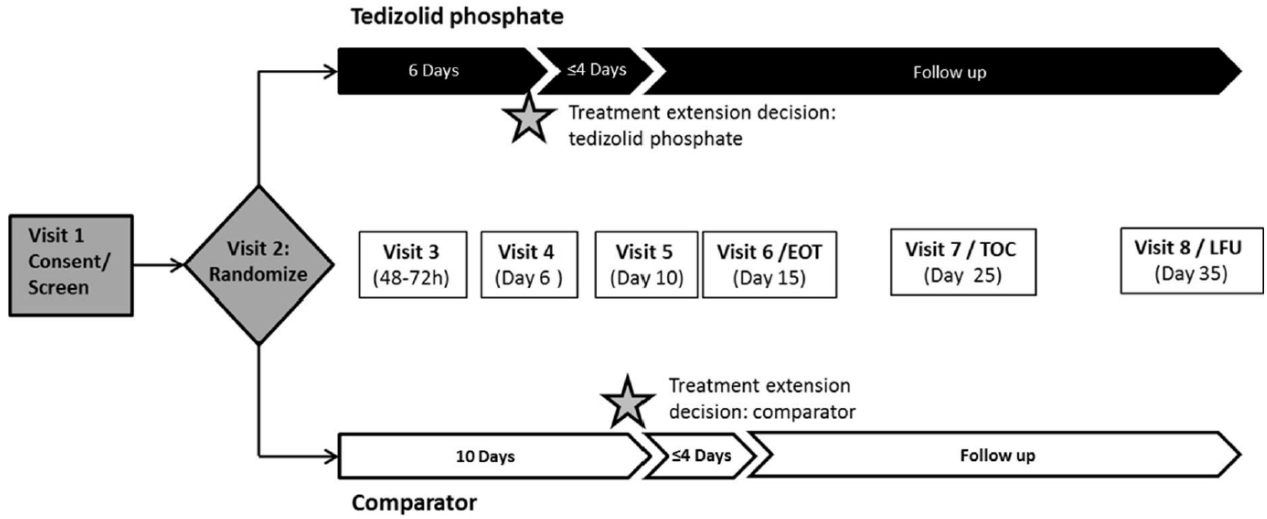
This study was a randomized (3:1 ratio), active controlled, parallel-group, multisite, assessor-blinded Phase 3 study to assess the safety and efficacy of tedizolid phosphate (IV and/or oral) versus protocol-

specified active comparators (IV and/or oral) for the treatment of ABSSSI in participants aged birth to <12 years with ABSSSI. Subjects were to be enrolled into four cohorts based on age:

- Cohort 1: 6 to <12 years of age;
- Cohort 2: 2 to <6 years of age;
- Cohort 3: 28 days to <2 years of age.

No participants were enrolled in Cohort 4 [<28 days].

A schematic of the study design for Study 208580 is presented in the following figure.



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

Study participants

Eligible participants were male or female aged birth (≥ 26 weeks gestational age at birth) to < 12 years with ABSSSI requiring antibiotic therapy and caused by a suspected or documented gram-positive pathogen(s). Patients with bacteremia, severe sepsis, or septic shock at the Screening visit were excluded.

The CHMP considered that the inclusion and exclusion criteria allowed the participation of children < 12 years with ABSSSI caused by Gram-positives, which is considered appropriate.

Treatments

The study interventions are presented in the following table.

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
Tedizolid Phosphate	Tedizolid Phosphate	IV: Refer to product labeling Oral: 20 mg/mL	200 mg	IV or oral	Once-daily, single 200-mg dose (body weight ≥50 kg), for 6 to 10 days	Test Product
Tedizolid Phosphate	Tedizolid Phosphate	IV: Refer to product labeling Oral: 20 mg/mL	2 mg/kg	IV or oral	Twice-daily (q12h) 2 mg /kg doses (body weight ≥30 to <50 kg), for 6 to 10 days	Test Product
Tedizolid Phosphate	Tedizolid Phosphate	IV: Refer to product labeling Oral: 20 mg/mL	2.5 mg/kg	IV or oral	Twice-daily (q12h) 2.5 mg /kg doses (body weight ≥3.2 to <30 kg), for 6 to 10 days	Test Product
Comparator	Vancomycin	Refer to product labeling	10 mg/kg with goal trough level of 10 to 15 mcg/mL	IV	Every 6 to 8 hours, for 10 to 14 days	Comparator
Comparator	Cephazolin (Cefazolin)	Refer to product labeling	50 or 100 mg/kg/day (up to 1,000 mg/dose)	IV	Every 6 to 8 hours, for 10 to 14 days	Comparator
Comparator	Linezolid	Refer to product labeling	10 mg/kg/dose (up to maximum dose 600 mg)	IV or oral	Every 6 to 8 hours, for 10 to 14 days	Comparator
Comparator	Clindamycin	Refer to product labeling	IV: 30 mg/kg/day (up to 600 mg/dose) Oral: 30 mg/kg/day (up to 450 mg/dose)	IV or oral	3 times daily, for 10 to 14 days	Comparator
Comparator	Flucloxacillin	Refer to product labeling	IV: 125 to 250 mg (2 to 10 years) or 62.5 to 125 mg (<2 years) Oral: 125 mg (2 to 10 years) or 62.5 mg (<2 years)	IV or oral	Every 6 hours, for 10 to 14 days	Comparator
Comparator	Cephalexin (Cefalexin)	Refer to product labeling	25 to 50 mg/kg/day (up to 500 mg/dose)	Oral	Every 6 to 12 hours, for 10 to 14 days	Comparator

The CHMP noted that the Tedizolid's posology was adjusted to body weight and the comparators are antibacterials active against Gram-positive agents.

Objectives

Primary objective

Use descriptive statistics to evaluate the safety of IV and/or oral 6 to 10-day tedizolid phosphate with 10 to 14-day IV and/or oral comparator in subjects from birth to <12 years of age with ABSSSI. No formal hypothesis tests will be used to evaluate this endpoint.

Secondary Objective

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

Tertiary/Exploratory Objectives

Use descriptive statistics to evaluate the programmatic early clinical response in the tedizolid phosphate and comparator groups at the 48 to 72 hour visit in subjects who remain hospitalized in the ITT population.

To characterize the population pharmacokinetics of tedizolid in subjects from birth to <12 years of age.

To characterize the acceptability and palatability of tedizolid phosphate oral suspension.

To use descriptive statistics to evaluate the microbiological outcomes in the tedizolid phosphate and comparator groups at the TOC visit in the Microbiological ITT (MITT) and Microbiologically Evaluable (ME) populations, including: Per-pathogen microbiological response at the TOC visit in the MITT and ME populations Per-subject microbiological response at the TOC visit in the MITT and ME populations.

To use descriptive statistics to evaluate the investigator's assessment of clinical success in the tedizolid phosphate and comparator groups at the TOC visit in the MITT and ME populations, overall and by-pathogen.

To describe recovery or progression of infection including changes from baseline in lesion size, assessment of signs and symptoms, and regional or systemic signs (lymphadenopathy, temperature, percentage immature neutrophils, white blood cell [WBC] count), and subject reported outcome (as Wong-Baker pain score).

The CHMP considered that, as this study is to be used to extrapolate efficacy and safety in adults to the paediatric population <12 years of age based on the exposure of tedizolid, the objectives were appropriately chosen. The primary objectives are related to safety.

Efficacy is a secondary objective. This is agreed upon by the Committee as efficacy will only be used to support PK and safety data towards the approval for the additional population.

Outcomes/endpoints

The primary study endpoint is related to safety; there were no primary efficacy endpoints. The secondary efficacy endpoint summarized in this document include:

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

Additional efficacy endpoints were categorized as Tertiary/Exploratory Endpoints and these include:

- Programmatic early clinical response in the tedizolid phosphate and comparator groups at the 48 to 72-hour visit.
- Characterization of the microbiological response of tedizolid phosphate and comparator groups in subjects with pathogens cultured at baseline. Assessment of microbiological outcomes programmatically using microbiological data from samples obtained at the TOC visit (both by-subject and by-pathogen).
- The investigator’s assessment of clinical response at the TOC visit, 22-29 days after the first infusion, in the MITT and ME populations.

- Measurement, assessment and recording of the primary lesion for signs and symptoms of ABSSSI and clinical response.

The CHMP considered that the efficacy endpoints were adequate.

Sample size

The planned enrolment was 100 participants to ensure at least 75 participants receive tedizolid phosphate and were evaluable for safety, with approximately 25 receiving comparator.

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

The sample size was mainly driven by safety considerations, which was considered acceptable by the CHMP.

Randomisation and Blinding (masking)

Treatment allocation/randomization occurred centrally using an interactive response technology (IRT).

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

Statistical methods

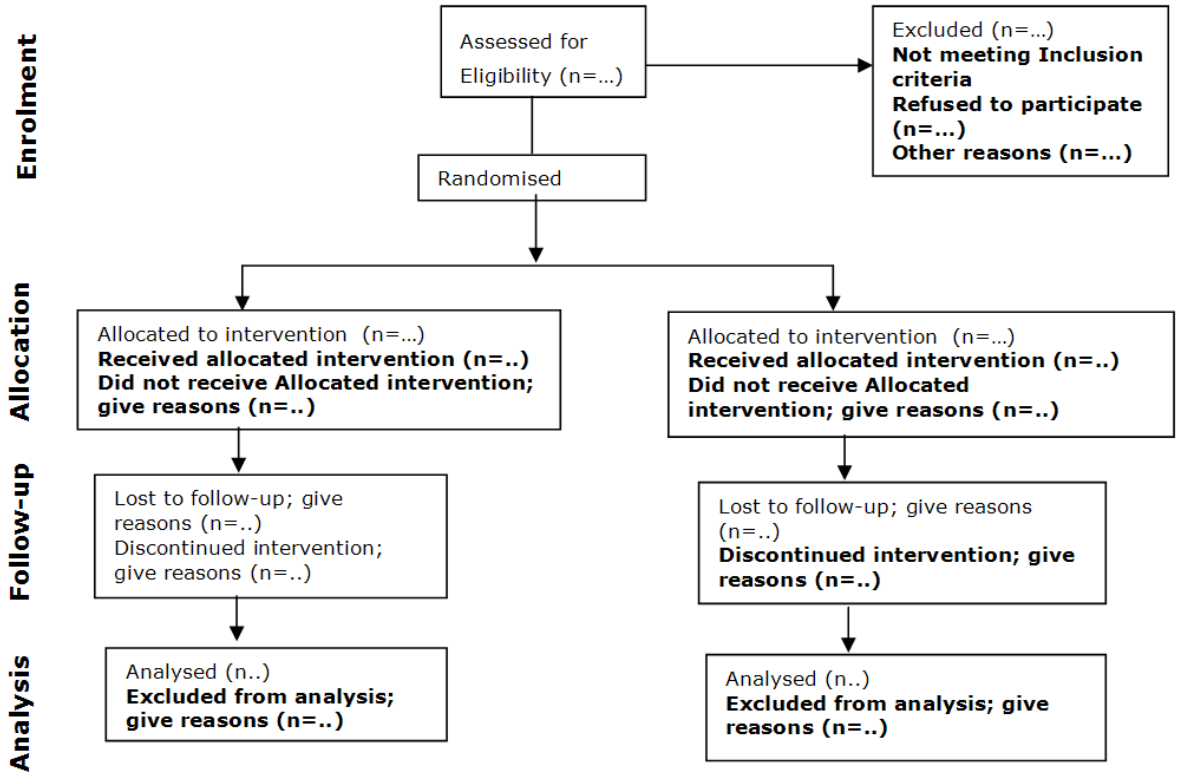
Descriptive statistics for safety/tolerability and efficacy assessments, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minima, and maxima for continuous variables were provided. For demographic and baseline disease characteristics, descriptive statistics were used to assess the comparability of the groups for each relevant characteristic. No statistical hypothesis tests were performed on these characteristics.

For the primary objective, the frequency, severity, and relationship to treatment of AEs were tabulated by System Organ Class and Preferred Term for each group. In addition, changes from baseline, shifts in toxicity grade, and substantially abnormal clinical laboratory values were summarized for each group.

For the secondary efficacy endpoint, the investigator's assessment of clinical response at the TOC visit was assessed in the ITT and CE-TOC populations using an exact 2-sided 95% CI for the clinical success rate (per blinded investigator's assessment) in each group using the Clopper-Pearson method. The difference in clinical success rate between groups was estimated using a 2-sided 95% CI for the treatment difference using the unstratified method of Miettinen and Nurminen.

Results

Participant flow



Recruitment

Clinical investigator study sites were located in 14 countries: Brazil, Bulgaria, Georgia, Germany, Guatemala, Latvia, Lithuania, Mexico, Poland, Russia, South Africa, Turkey, Ukraine, and USA.

The first participant was enrolled on 20 January 2019 and the last visit of the last patient was on 6 July 2023.

Conduct of the study

Protocol amendments

The original protocol was amended 7 times. The changes implemented in the protocol are summarized in the following table:

Document	Date of Issue	Overall Rationale
Amendment 7	27-JUN-2022	Added a potential interim analysis for the 2 Cohorts spanning 2 to <12 years of age in order to support a possible regulatory filing for this age group in light of the slower enrollment of children <2 years of age; reduced the sample size from 120 to 100; and revised eligibility criterion regarding allowed duration of prior antibiotic treatment.
Amendment 6	24-MAY-2021	Eliminated certain eligibility constraints and reduced the number of required in-person visits in order to improve feasibility to enroll outpatients.
Amendment 5	16-SEP-2020	Preplanned addition of dose levels for children 28 days to <2 years of age (Cohort 3) based on updated modeling and simulation using newly available data from ongoing studies; addition of country specific eligibility requirements; and addition of study termination criteria and data protection policies.
Amendment 4	03-OCT-2019	Dosing adjustment due to a preplanned analysis.
Amendment 3	20-SEP-2018	Dose adjustment including modification to q12h dosing; modified extension of treatment to allow 1-4 days of extension (not fixed at 4 days' extension); added recommendations for comparator dosing; modification of IC/EC; modification of procedures e.g. PK sampling to account for twice-daily dosing regimen.
Amendment 2	13-APR-2018	Reduced minimum age to birth; clarification of minimum sample sizes in each age group.
Amendment 1	10-AUG-2017	Dose adjustment, addition of excluded medications, modification of IC/EC.
Original Protocol	25-JUL-2016	Not applicable.

Protocol deviations

Important protocol deviations were reported for 34 participants. Of these, 2 participants had important protocol deviations that were considered to be clinically important. Overall, 33 participants had important protocol deviations that were not considered to be clinically important.

The most common deviation types were trial procedures and study interventions deviations reported for 25 (74%) and 8 (24%) of the 34 participants with protocol deviations, respectively. Out of window visits were reported for 23 participants.

The 2 participants that had important protocol deviations that were considered to be clinically important were included in the tedizolid arm:

- One participant received study drug that was expired or damaged (such as reconstituted IV study drug was not administered within 24 hours) and
- One participant missed safety laboratory assessment (entire panel of either chemistry or hematology or both) from Visit 1, or both Visit 4 or 6.

One participant had a not important Inclusion/ Exclusion Criteria deviation associated with the COVID-19 pandemic.

Baseline data

Overall, the mean age of participants (based on APaT) was 6.0 years; approximately half of the participants were male, and the majority were white, reflecting the demographic characteristics of the regions where enrolment was greatest. Demographic characteristics were generally comparable between both groups, although there was a higher percentage of participants in the comparator group that were inpatient at baseline (80% in the tedizolid group vs. 96% in the comparator group).

The most commonly reported type of ABSSSI at baseline was subcutaneous abscess, representing just over half the population in both groups. The mean lesion surface area of the ABSSSI at baseline was comparable between both groups (60.9 cm^2 in tedizolid group and 65.4 cm^2 in the comparator group).

The most commonly reported signs and symptoms of ABSSSI present at the baseline visit were localized warmth and tenderness on palpation. Most participants had moderate to severe signs and symptoms of erythema (62%) and tenderness on palpation (75%).

	Tedizolid		Comparator		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	75		25		100	
Sex						
Male	40	(53.3)	13	(52.0)	53	(53.0)
Female	35	(46.7)	12	(48.0)	47	(47.0)
Age (Years)						
6 to < 12 years	44	(58.7)	15	(60.0)	59	(59.0)
2 to < 6 years	16	(21.3)	5	(20.0)	21	(21.0)
28 days to < 2 years	15	(20.0)	5	(20.0)	20	(20.0)
Participants with data	75		25		100	
Mean	5.9		6.4		6.0	
SD	3.59		3.78		3.63	
Median	7.0		8.0		7.0	
Range	0.3 to 11.0		0.8 to 11.0		0.3 to 11.0	

Race						
American Indian Or Alaska Native	1	(1.3)	0	(0.0)	1	(1.0)
Black Or African American	10	(13.3)	1	(4.0)	11	(11.0)
White	58	(77.3)	22	(88.0)	80	(80.0)
Multiple	6	(8.0)	2	(8.0)	8	(8.0)
Ethnicity						
Hispanic Or Latino	13	(17.3)	4	(16.0)	17	(17.0)
Not Hispanic Or Latino	62	(82.7)	21	(84.0)	83	(83.0)
Height (cm)						
Participants with data	75		25		100	
Mean	112.9		119.3		114.5	
SD	27.32		30.02		28.00	
Median	124.0		127.0		124.0	
Range	51.0 to 154.0		66.0 to 162.0		51.0 to 162.0	
Weight (kg)						
Participants with data	75		25		100	
Mean	23.8		26.4		24.5	
SD	12.69		15.79		13.49	
Median	22.0		24.0		23.0	
Range	6.0 to 59.0		8.0 to 68.0		6.0 to 68.0	
Body Mass Index (kg/m²)						
Participants with data	75		25		100	
Mean	17.63		17.14		17.51	
SD	3.631		4.124		3.745	
Median	17.35		15.91		17.32	
Range	10.65 to 27.04		9.91 to 25.91		9.91 to 27.04	
Geographic Region						
Europe, Middle East and Africa	63	(84.0)	22	(88.0)	85	(85.0)
Latin America	12	(16.0)	3	(12.0)	15	(15.0)
Status at Baseline						
Inpatient	60	(80.0)	24	(96.0)	84	(84.0)
Outpatient	15	(20.0)	1	(4.0)	16	(16.0)
Type of Infection						
Cellulitis	19	(25.3)	6	(24.0)	25	(25.0)
Erysipelas	0	(0.0)	1	(4.0)	1	(1.0)
Subcutaneous abscess	40	(53.3)	14	(56.0)	54	(54.0)
Wound infection	16	(21.3)	4	(16.0)	20	(20.0)
Lesion Surface Area (cm²)						
Participants with data	75		25		100	
Mean	60.9		65.4		62.0	
SD	143.97		95.96		133.15	
Median	27.0		51.0		28.4	
Range	2.0 to 1068.0		9.0 to 480.0		2.0 to 1068.0	

Prior Antibiotics						
Yes	17	(22.7)	5	(20.0)	22	(22.0)
No	58	(77.3)	20	(80.0)	78	(78.0)
Baseline Culture						
Positive	52	(69.3)	14	(56.0)	66	(66.0)
Negative	5	(6.7)	6	(24.0)	11	(11.0)
Unknown	18	(24.0)	5	(20.0)	23	(23.0)

SD=Standard deviation.

Note: Age was derived in years with 3 decimals, from data collected in years and months when participants were randomized. For participants less than 3 months old the number of days postnatal were collected and the age was also derived in years. (Example: The age in years of a 7 day old was derived as 7/365 = 0.0191 years.)

BMI is calculated as Baseline Weight/(Baseline Height/100)^2.

Baseline Microbiology

The baseline microbiological assessments of the primary infection site were comparable between groups. Based on Gram stain, the majority of specimens in each group (between ~58% and 88% of samples in the APaT population with available data) contained gram-positive cocci.

Consistent with the epidemiology of ABSSSI, the most commonly isolated gram-positive pathogen at baseline in each of the groups in the MITT population was *S. aureus*, (>82% in both groups), consisting primarily of MSSA isolates.

	Tedizolid		Comparator		Total	
Pathogenic Organism	n	(%)	n	(%)	n	(%)
Participants in population	46		14		60	
Staphylococcus aureus	38	(82.6)	12	(85.7)	50	(83.3)
MRSA	3	(6.5)	1	(7.1)	4	(6.7)
MSSA	32	(69.6)	11	(78.6)	43	(71.7)
Enterococcus faecalis	3	(6.5)	1	(7.1)	4	(6.7)
Enterococcus faecium	2	(4.3)	1	(7.1)	3	(5.0)
Staphylococcus haemolyticus	2	(4.3)	0	(0.0)	2	(3.3)
Streptococcus pyogenes	2	(4.3)	0	(0.0)	2	(3.3)
Streptococcus anginosus group	0	(0.0)	1	(7.1)	1	(1.7)
Streptococcus constellatus	2	(4.3)	0	(0.0)	2	(3.3)
Group C beta hemolytic streptococcus	1	(2.2)	0	(0.0)	1	(1.7)

Note: ABSSSI = Acute bacterial skin and skin infections; MRSA = Methicillin-resistant *Staphylococcus aureus;* MSSA = Methicillin-sensitive *Staphylococcus aureus.*

Results in the ME population were comparable with those described for the MITT population.

The CHMP considered that even if no participants < 28 days of age were included, no significant differences in efficacy in this age group were expected.

Numbers analysed

Of the 100 participants allocated, 100 were included in the ITT population, which defined the population evaluable for efficacy analysis of tedizolid, and all 100 were included in the APaT population for safety analysis.

As of the DBL, 44 participants in Cohort 1, 16 participants in Cohort 2, and 15 participants in Cohort 3 received tedizolid phosphate. No participants were enrolled in Cohort 4 [<28 days].

Outcomes and estimation

- Primary Efficacy Endpoint

There was no primary efficacy endpoint for this study.

- Secondary Efficacy Endpoint

Clinical Response at the TOC Visit on Day 25 (ITT and CE-TOC Populations)

The clinical success rates at the TOC visit (22 to 29 days after first dose) were high (>90%) and comparable between the tedizolid and comparator groups in both the ITT and CE-TOC populations.

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

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

	Tedizolid			Comparator			Estimated	
Clinical Response	n	(%)	95% CI[a]	n	(%)	95% CI[a]	Difference (%)[b]	95% CI[b]
Clinical Response (EOT)								
Number of Participants	68			23				
Clinical Success	68	(100.0)	(94.7, 100.0)	23	(100.0)	(85.2, 100.0)	0.0	(0.0, 0.0)
Clinical Failure or Indeterminate	0	(0.0)		0	(0.0)			
Clinical Failure	0	(0.0)		0	(0.0)			
Indeterminate	0	(0.0)		0	(0.0)			
Clinical Response (TOC)								
Number of Participants	68			23				
Clinical Success	68	(100.0)	(94.7, 100.0)	23	(100.0)	(85.2, 100.0)	0.0	(0.0, 0.0)
Clinical Failure or Indeterminate	0	(0.0)		0	(0.0)			
Clinical Failure	0	(0.0)		0	(0.0)			
Indeterminate	0	(0.0)		0	(0.0)			

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

Clinical success rates were also >90% for both groups at the earlier timepoint of EOT, with no clinical failures, although there were more indeterminates (due to missing data) in the tedizolid versus comparator group.

A sensitivity analysis in the ITT population considered all participants with an indeterminate response or missing data as clinical success. The clinical success rates using this approach were 100% in both groups.

The CHMP considered that the high clinical success rates in the tedizolid and comparator groups provided reassurance of an adequate efficacy of tedizolid in the age groups included in the sought extension of indication.

- Other Efficacy Endpoints

Early Clinical Response at the 48 to 72 Hour Visit (ITT Population)

The programmatic early clinical response rates at the 48 to 72 hour visit were high (≥80%) and comparable for both the tedizolid and comparator groups in the ITT population.

Of note, as of protocol amendment 6, the 48 to 72 hour visit could be conducted by telephone if the participant had been discharged from the hospital. Therefore, the early clinical response was not available for 11 participants due to lack of lesion size measurements at this time point.

Early Clinical Response at 48-72 Hour	Tedizolid			Comparator			Estimated Difference (%)[b]	95% CI[b]
	n	(%)	95% CI[a]	n	(%)	95% CI[a]		
Number of Participants	75			25				
Success/Responder	60	(80.0)	(69.2, 88.4)	21	(84.0)	(63.9, 95.5)	-4.0	(-21.0, 13.0)
Failure/Nonresponder	4	(5.3)		4	(16.0)			
Indeterminate	11	(14.7)		0	(0.0)			

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

The programmatic early clinical response rates were consistent with those seen at the TOC visit.

- Assessment of Acceptability/Palatability of Oral Tedizolid Phosphate Oral Suspension

Seventy of the 75 participants in the tedizolid group received the oral formulation (either initially or after having received the IV formulation) and rated its acceptability/palatability at the time of the first dose. A majority (>60%) of participants (or observers, where applicable) (45/70) rated acceptability/palatability to be either "Good" or "Very Good". Few participants (7/70) rated acceptability/palatability to be "Bad" or "Very Bad".

- Rate of Relapse, Superinfection, and New Infection

In the CE-TOC population, all participants had a baseline ABSSSI categorized as a clinical success at the TOC visit. No events of relapse were reported.

No participant in either group was diagnosed with a superinfection or a new infection at the TOC visit. One participant in the tedizolid group who had a clinical response at EOT was classified as indeterminate at TOC with an AE of skin infection starting 1 day prior, due to a living situation that placed them at high risk of repeated infections.

- Microbiological Outcomes

Microbiological Response at Test-of-Cure (TOC) Visit on Day 25 (MITT and ME Populations)

The microbiological response rate (eradication or presumed eradication) at the TOC visit was high and comparable for both groups, in both MITT (97.8% and 100%, respectively) and ME (100% for both groups) populations. This was observed on a per-pathogen and a per participant basis. On a per-pathogen basis, response rates for *S. aureus*, the most prevalent pathogen, were 97.4% and 100% in the tedizolid and comparator group MITT population, respectively.

The microbiological response rates were driven by responses to S. aureus. Response rates for other bacterial species could not be compared between groups due to the small numbers of participants infected with species other than S. aureus. In the MITT populations, microbiological response rates were 100% regardless of pathogen or MIC.

Clinical Response at the TOC Visit on Day 25 (MITT and ME Populations)

The clinical success rates at the TOC visit (22 to 29 days after first dose) were high (>97%) and comparable between the tedizolid and comparator groups, in both the MITT and ME populations.

The per-pathogen clinical success rates were consistent with the per-pathogen microbiological response rates in both groups using the MITT and ME populations.

In the MITT and ME populations, clinical success rates were 100% regardless of pathogen or MIC.

Changes from Baseline in Lesion Area and Symptoms (ITT Population)

Substantive decreases in mean lesion surface area from baseline were seen at the 48 to 72 hour visit in both the tedizolid and comparator groups, with the mean area decreasing by 48.7 cm^2 in the tedizolid group and 41.0 cm^2 in the comparator group. Decreases from baseline in mean lesion surface area remained comparable in the tedizolid and comparator groups across visits through the TOC visit, with a plateau in rate of decrease seen at the Day 10 visit. The mean percent change in surface area was >95% for both groups by the Day 10 visit.

The changes in the signs and symptoms of the primary ABSSSI from the Screening visit to the EOT visit were comparable across study intervention groups. Most signs and symptoms were absent at the EOT visit in the majority (>90%) of participants (for whom data were available at both Screening and EOT visits) in both study intervention groups.

At EOT and TOC no signs or symptoms reported were moderate or severe. Induration was present for less than 10% of participants in either group at EOT and TOC.

Participant-reported Assessment of Pain

The mean pain intensity ratings reported by participants, based on the Wong-Baker FACES pain rating scale, were comparable for both groups at each visit. The mean pain intensities reported in the tedizolid and comparator groups were 8.1 and 7.4 at baseline and 0.1 for both groups at the EOT visit.

Summary of main study

The following table summarises the efficacy results from the study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10. Summary of Efficacy for trial MK-1986-018

Title: A Phase 3 Randomized, Active-comparator-controlled Clinical Trial to Study the Safety and Efficacy of MK-1986 (Tedizolid Phosphate) and Comparator in Subjects from Birth to less than 12 Years of Age with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)		
Study identifier	Study MK-1986-018	
Design	Phase 3, multicenter, randomized, active-comparator-controlled study	
	Duration of main phase: Duration of follow-up: Duration of Extension phase:	Tedizolid: up to 10 days; Comparator: up to 14 days 35 days not applicable
Hypothesis	No hypothesis tested	
Treatments groups	Tedizolid	Tedizolid. 6 to 10 days, N=75
	Comparator	Other antibacterial agents. 10 to 14 days, N=25

Endpoints and definitions	Primary endpoint	Safety	Safety of tedizolid versus comparator in the paediatric population
	Secondary endpoint	Efficacy	Investigator's assessment of clinical response at the TOC visit in the ITT and CE-TOC populations
	Exploratory endpoint	Efficacy	Programmatic early clinical response at the 48 to 72-hour visit.
	Exploratory endpoint	PK	Evaluation of PK endpoints to characterize the population PK of tedizolid in subjects from birth to <12 years of age
	Exploratory endpoint	other	Single Assessment of acceptability and palatability of the tedizolid phosphate oral suspension
	Exploratory endpoint	Efficacy	Microbiological response in subjects with pathogens cultured at baseline
	Exploratory endpoint	Efficacy	Investigator's assessment of clinical response at the TOC visit in the MITT and ME populations
	Exploratory endpoint	Efficacy	Measurement, assessment and recording of the primary lesion
Database lock	13 September 2023		

Results and Analysis

Analysis description	**Main efficacy analysis**		
Analysis population and time point description	Intent to treat Test-of-cure, 25 days		
Descriptive statistics and estimate variability	Treatment group	Tedizolid	Comparator
	Number of subject	75	25
	Clinical Success n (%)	70 (93.3%)	23 (92.0%)
	95% CI	(85.1, 97.8)	(74.0, 99.0)

2.4.2. Discussion on clinical efficacy

The aim of the application is to extend the current approved Sivextro indication to allow the use of tedizolid in children from birth to <12 years of age.

The clinical data submitted to support the proposed extension of the indication consists of:

- The analysis of the PK, safety, and efficacy data of tedizolid in children from birth to <12 years of age from Study MK-1986-018.

Design and conduct of clinical study

The study was not powered for a precise estimate of efficacy even if a comparator arm was included for comparison. Tedizolid's posology was adjusted to body weight and the comparators are antibacterials active against Gram-positive agents.

The study population consisted of patients <12 years of age with ABSSSI distributed in 4 cohorts according to predefined age groups (no patient was included in cohort 4: <28 days)

Efficacy data and additional analyses

The clinical success rates at the TOC visit (22 to 29 days after first dose) were high (>90%) and comparable in the tedizolid and comparator groups in both the ITT (all randomized participants) and CE-TOC populations.

Clinical success rates were also >90% for both groups at the earlier timepoint of EOT, with no clinical failures, although there was a higher percentage of indeterminates (due to missing data) in the tedizolid vs comparator group (4/75 [5.3%] vs 0/25 [0%]).

Clinical success rates were 100% in both groups based on a sensitivity analysis (ITT population), which considered all participants with an indeterminate response or missing data as a clinical success.

The microbiological response rate (eradication or presumed eradication) at the TOC visit was high and comparable for both groups, in both MITT (97.8% and 100%, respectively) and ME (100% for both groups) populations.

The high clinical success rates in the tedizolid and comparator groups provide reassurance of an adequate efficacy of tedizolid in the age groups included in the sought extension of indication.

2.4.3. Conclusions on the clinical efficacy

While the phase 3 study was not planned to evaluate efficacy as a primary objective, the efficacy results support the extension of the indication of Sivextro to patients <12 years of age.

2.5. Clinical safety

Introduction

The development programme for the paediatric population <12 years of age included 3 (2 Phase 1 and 1 Phase 3) clinical studies. The 2 Phase 1 studies, MK1986013 (P013) and MK1986014 (P014), evaluated the PK, safety, and tolerability of a single oral or IV dose of tedizolid phosphate in participants 2 to <12 years of age (P013) and birth to <2 years of age (P014). P014 also included multipledose neonatal (full-term and preterm neonates from birth to <28 days of age) cohorts to evaluate the PK, safety, and tolerability of multiple IV doses of tedizolid phosphate in the neonatal age group. The Phase 3 study, MK-1986-018 (P018), evaluated the safety and efficacy of multiple oral and IV doses of tedizolid phosphate in participants <12 years of age. The 3 paediatric studies provide safety data in the population <12 years of age to permit bridging from adolescents and adults.

Table 11 - Summary of Clinical Safety Studies with Tedizolid Phosphate in Participants <12 Years of Age

Study Number (Status) [CTD Location] **Number of Study Sites (Regions)**	**Design (Indication)**	**Dosing Regimen[a,b,c]**	**Study Population (N)[c]**
Phase 3 Study (Participants <12 Years)			
MK-1986-018 (completed) [Ref. 5.3.5.1: P018MK1986]	Randomized (tedizolid phosphate:	Tedizolid phosphate (n=75) for 6 to 10 days[d] IV and/or PO:	Gender: 53M/47F

Study Number (Status) [CTD Location] **Number of Study Sites (Regions)**	**Design (Indication)**	**Dosing Regimen[a,b,c]**	**Study Population (N)[c]**
20 sites (4 regions)	comparator 3:1), assessor-blind, active-controlled, multicenter, parallel-group, intervention study Indication: ABSSSI	• once daily 200 mg (body weight ≥50 kg) • q12h 2 mg/kg (body weight ≥30 to <50 kg) • q12h 2.5 mg/kg (body weight ≥3.2 to <30 kg) Comparator (n=25) for 10 to 14 days[d] IV and/or PO from allowed list per local standard of care (per product labeling)[e]	Age: 28 days to <12 years N=100 in the following age cohorts: • 6 to <12 years (n=59) • 2 to <6 years (n=21) • 28 days to <2 years (n=20) • From birth to <28 days (none enrolled in this planned cohort) Participants with ABSSSI
Phase 1 Studies (Participants <12 Years)			
MK-1986-013 (completed) [Ref. 5.3.3.2: P013MK1986] 15 sites (3 regions)	Nonrandomized, open-label, uncontrolled, multicenter, 2part, SD study Indication: Bacterial infection (no efficacy endpoints)	Tedizolid phosphate SD IV: • 6 to <12 years: 5 mg/kg (n=5) or 4 mg/kg (n=5) • 2 to <6 years: 6 mg/kg (n=5) or 3 mg/kg (n=5) Tedizolid phosphate SD PO: • 6 to <12 years: 4 mg/kg (n=6) • 2 to <6 years: 3 mg/kg (n=6)	Gender: 19M/13F Age: 2 to <12 years N=32 in the following age groups: • 6 to <12 years (n=16) • 2 to <6 years (n=16) Hospitalized participants receiving prophylaxis for or with a confirmed or suspected infection with gram-positive bacteria and receiving concurrent antibiotic treatment with gram-positive antibacterial activity

Study Number (Status) [CTD Location] **Number of Study Sites (Regions)**	**Design (Indication)**	**Dosing Regimen[a,b,c]**	**Study Population (N)[c]**
MK-1986-014 (completed) [Ref. 5.3.3.2: P014MK1986] 17 sites (3 regions)	Nonrandomized, open-label, uncontrolled, multicenter, 2part, SD and MD intervention study Indication: Bacterial infection (no efficacy endpoints)	Tedizolid phosphate 3 mg/kg (body weight <10 kg) or 2.5 mg/kg (body weight 10 to <30 kg): SD IV: • 28 days to <6 months (n=4) • 6 months to <24 months (n=6) • From birth to <28 days: Full-term neonates (n=8), Preterm neonates (n=9) MD IV twice daily for 3 days: • From birth to <28 days: Full-term neonates (n=4), Preterm neonates (n=4) SD PO: • 28 days to <24 months (n=4) • From birth to <28 days: Full-term neonates (n=4), Preterm neonates (n=4)	Gender: 29M/18F Age: Birth to <24 months N=47 in the following age groups: • 28 days to <24 months (n=14) • From birth to <28 days: Fullterm neonates (n=16), Preterm neonates (n=17) Hospitalized participants receiving prophylaxis or treatment for a confirmed or suspected infection with gram-positive bacteria

ABSSSI=acute bacterial skin and skin structure infection; CTD=Common Technical Document; EU=European Union; F=female; IAs=interim analyses; IV=intravenous; M=male; M&S=modeling and simulation; MD=multiple-dose; MK1986=tedizolid phosphate (SIVEXTRO™); N=number of participants who received ≥1 dose of study intervention in the study; n=number of participants in the age cohort/group who received ≥1 dose of study intervention in the dosing or age cohort/group; PK=pharmacokinetic(s); PO=oral; q12h=every 12 hours; SD=single-dose.

[a] For all studies, IV doses were administered as an IV infusion over approximately 1 hour.
[b] Dose modifications were performed during the studies based on PK IAs and M&S analyses.
[c] Age group and age cohort are used interchangeably. Age is at time of consent. Participants 28 days to <2 years of age were preterm or full-term at birth. Full-term neonates were born ≥37th week of gestation. Preterm neonates were born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.
[d] In P018, treatment duration could have been prolonged up to a maximum of 10 days of tedizolid phosphate or 14 days of comparator, if clinically indicated based on blinded investigator assessment at Visit 4 (~Day 6 of dosing) in the tedizolid group or Visit 5 (~Day 10 of dosing) in the comparator group.
[e] Allowed IV comparators in P018 were vancomycin, linezolid (outside the EU only, as it is not approved for paediatric use in the EU), clindamycin, flucloxacillin, and cephazolin (cefazolin). Allowed oral comparators were linezolid (outside the EU only), clindamycin, flucloxacillin, and cephalexin (cefalexin).

Safety results from P013, P014, and P018 were presented by individual study. Additionally, safety results from the multiple-dose cohorts of P014 and from P018 were pooled with safety results from a multiple-dose Phase 3 study MK-1986-012 (P012, previously submitted as part of a prior application to support an extension of indication to the adolescent population) in adolescents 12 to <18 years of age with ABSSSI. Pooled safety tables presented provide an analysis of the safety and tolerability of IV and oral tedizolid phosphate by age group for a combined population of participants from birth to <18 years of age in the 3 multiple-dose studies. The pooled tables also provide an analysis of the safety and tolerability of IV and oral tedizolid phosphate (tedizolid group) vs investigator's choice of comparator from a specified list of allowed comparators, used in accordance with local standard of care (comparator group) for a combined population of participants 28 days to <18 years of age in the comparator-controlled studies (P012, P018). Allowed IV comparators were vancomycin, linezolid (outside the EU only, as it is not approved for paediatric use in the EU), clindamycin, flucloxacillin, and cephazolin

(cefazolin). Allowed oral comparators were linezolid (outside the EU only), clindamycin, flucloxacillin, and cephalexin (cefalexin). Neonates were not included in the analysis of tedizolid phosphate vs comparator because there was no comparator group in P014.

The same IV formulation of tedizolid phosphate was administered to participants <12 years of age (P013, P014, P018) as was administered to adolescent participants 12 to <18 years of age (P012). The oral 200 mg tablet was used in adolescent participants (P012) and an age-appropriate, weight-based oral suspension dose was used in all 3 studies in participants <12 years of age. Results were pooled without regard to route of administration (IV or oral) as similar PK exposures were expected due to the high bioavailability of the oral formulations. P014 and P018 had weight-based dosing to achieve steady-state exposures in participants <12 years of age that were generally comparable to those observed in adults and adolescents (P012), which allowed pooling without regard to dosing regimen or treatment duration.

Safety and tolerability of tedizolid phosphate were evaluated in studies P013, P014, and P018 (as well as in the previously submitted study P012) using the APaT (all participants as treated) population, which included all participants who received ≥1 dose of study intervention. The assessments included AEs, vital signs, physical examinations (including specific neurological and visual acuity assessments in P018), and clinical laboratory assessments (haematology and clinical chemistry). No formal hypothesis tests were used to evaluate the safety endpoints.

Safety evaluations were conducted through the final planned study visit for each study (~7 days after the single dose of study intervention in P013, ~14 days after the last dose of study intervention in P014, or ~19 to 34 days after the last dose of study intervention in P018). AEs were recorded at each visit and assessed, followed up, and reported according to standard guidelines.

Clinical laboratory values outside the normal range that the investigator assessed to be clinically significant were reported as AEs. In studies with multiple dosing, abnormal laboratory values were also graded using the DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events v2 (P014) or v2.1 (P018 and the integrated data pool).

The CHMP noted that the development programme for the paediatric population <12 years of age included 3 clinical studies: 2 Phase 1 and 1 Phase 3. The 2 Phase 1 studies, P013 and P014, evaluated the PK, safety, and tolerability of a single oral or IV dose of tedizolid phosphate in participants 2 to <12 years of age (P013) and from birth to <2 years of age (P014). P014 also included multiple-dose neonatal (full-term and preterm neonates) cohorts to evaluate the PK, safety, and tolerability of multiple IV doses of tedizolid phosphate in the neonatal age group. In P014 study, no MD regimen was evaluated for patients aged 28 days to <24 months. The Phase 3 study (P018) evaluated the safety and efficacy of multiple IV and oral doses in participants <12 years of age. No patient from birth to < 28 days was enrolled in this study.

Safety results from P013, P014, and P018 were presented by individual study. Additionally, safety results from the multiple-dose cohorts of P014 and from P018 were pooled with safety results from a multiple-dose Phase 3 study MK-1986-012 (P012, previously submitted as part of a prior application to support an extension of indication to the adolescent population) in adolescents 12 to <18 years of age with ABSSSI, which was considered acceptable by the Committee.

Patient exposure

Disposition of Participants

Individual Studies (P013, P014, P018)

Overall, 154 participants <12 years of age received ≥1 dose of tedizolid phosphate in P013, P014, and P018, and 25 received ≥1 dose of comparator in P018.

In P013, all 32 allocated participants received a single dose of tedizolid phosphate. One participant completed study intervention per protocol but discontinued the study (lost to follow-up).

In P014, all 47 allocated participants received ≥1 dose of tedizolid phosphate. No participants discontinued study intervention or the study.

In P018, 100 randomized participants received ≥1 dose of study intervention (tedizolid group: 75; comparator group: 25). Most participants (tedizolid group: 71; comparator group: 23) completed both study intervention and the study. Six participants discontinued both study intervention and the study (tedizolid group: 4, all due to withdrawal by parent/guardian; comparator group: 2, both lost to follow-up).

Pooled Multiple-dose Studies (P012, P014, P018)

Overall, 174 participants <18 years of age received ≥1 dose of tedizolid phosphate in P012, P014, and P018, and 54 received ≥1 dose of comparator in P012 and P018, and were included in the safety data pool for the pooled multiple-dose paediatric studies [Table **12**].

Table 12 - Pooled Multiple-dose Pediatric Studies (P012, P014, P018) Safety Data Pool by Age Group

Study Number [CTD Location]	**Age Group(s)**		**Tedizolid Phosphate (N=174)**	**Comparator (N=54)**	**Total (N=228)**
MK-1986-012[a]	12 to <18 years		91	29	120
MK-1986-018 [Ref. 5.3.5.1: P018MK1986]	6 to <12 years		44	15	59
	2 to <6 years		16	5	21
	28 days to <2 years[b]		15	5	20
MK-1986-014 (Multipledose Cohorts) [Ref. 5.3.3.2: P014MK1986]	Birth to <28 days	Fullterm neonates[b]	4	NA	8
		Preterm neonates[b]	4		

Age group and age cohort are used interchangeably; CTD=Common Technical Document; N=overall number of participants in the treatment or age group; NA=not applicable.

a The P012 CSR was provided in a previous supplemental application for the adolescent ABSSSI indication.

b Preterm or at birth. Full-term neonates were born ≥37th week of gestation. Preterm neonates were born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

Duration of Exposure

Individual Studies (P013, P014, P018)

A total of 154 participants received ≥1 dose of tedizolid phosphate in P013, P014, and P018.

In P013, 32 participants received a single dose (20 IV and 12 oral) of tedizolid phosphate.

In P014, 39 participants received a single dose (27 IV and 12 oral) and 8 participants received multiple IV doses (twice daily for 3 days) of tedizolid phosphate.

In P018, 75 participants received multiple doses of tedizolid phosphate (5 IV only, 15 oral only, and 55 IV to oral) and 25 received multiple doses of comparator (7 IV only, 2 oral only, and 16 IV to oral); the mean duration of treatment was 7.5 to 8.7 days across age groups in the tedizolid group and 9.5 to 9.8 days across age groups in the comparator group, consistent with the protocol-specified treatment period for tedizolid phosphate (6 to 10 days) or comparator (10 to 14 days).

Pooled Multiple-Dose Studies (P012, P014, P018)

A total of 174 participants <18 years of age received ≥1 dose of tedizolid phosphate in P012, P014, and P018 and were included in the safety data pool for the pooled multiple-dose paediatric studies.

Demographic and Other Characteristics of Study Population

Individual Studies (P013, P014, P018)

Overall, other than the expected differences in age and weight across participants from birth to <12 years in the different age groups in the 3 studies, demographic and other baseline characteristics (including sex and race) were generally comparable for the 3 studies. Demographic and other baseline characteristics were comparable for the tedizolid and comparator groups in P018.

P014 had a higher (42.6%) proportion of Hispanic participants compared with P013 (34.4%) and P018 (17.0%).

The mean age (SD) of participants was 5.8 (2.6) years in P013, 88.8 (165.7) days in P014, and 6.0 (3.63) years in P018, and was comparable for the tedizolid and comparator groups in P018.

All participants in P013 and P014 were receiving treatment or prophylaxis for gram-positive bacterial infection and were hospitalized at baseline. Participants in P018 had ABSSSI due to a gram-positive pathogen and 84.0% were hospitalized at baseline (tedizolid group: 80%; comparator group: 96%).

In P018, 54.0% of participants (tedizolid: 53.3%; comparator: 56.0%) entered the study with subcutaneous abscess as their qualifying ABSSSI. The overall mean ABSSSI lesion surface area at baseline was 62.0 cm^2 (tedizolid group: 60.9 cm^2; comparator group: 65.4 cm^2).

Pooled Multiple-Dose Studies (P012, P014, P018)

Demographic and other baseline characteristics of the 228 participants from birth to <18 years of age in the pooled population were generally consistent with those in the individual studies (table above) and were comparable across treatment groups in the comparator-controlled studies (table below).

Appendix 2.7.4-absssichild: 9
Participant Characteristics
Pediatric (Pooled PN012, PN014, and PN018) Studies with Multiple Doses of Study Medication
Safety Analysis Set

	0 to <28 days Tedizolid		28 days to <2 years Tedizolid		2 to <12 years Tedizolid		12 to <18 years Tedizolid		28 days to <18 years Tedizolid		28 days to <18 years Comparator	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		15		60		91		166		54	
Sex												
Male	5	(62.5)	4	(26.7)	36	(60.0)	58	(63.7)	98	(59.0)	30	(55.6)
Female	3	(37.5)	11	(73.3)	24	(40.0)	33	(36.3)	68	(41.0)	24	(44.4)
Age (Years)												
Participants with data	8		15		60		91		166		54	
Mean	0.0		1.1		7.1		14.4		10.6		10.7	
SD	0.02		0.48		2.87		1.69		5.03		4.93	
Median	0.0		1.1		7.0		15.0		12.0		12.0	
Range	0.0 to 0.1		0.4 to 2.0		2.0 to 11.0		12.0 to 17.0		0.4 to 17.0		0.8 to 17.0	
Race												
American Indian Or Alaska Native	1	(12.5)	1	(6.7)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
Asian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Black Or African American	0	(0.0)	9	(60.0)	1	(1.7)	11	(12.1)	21	(12.7)	5	(9.3)
White	3	(37.5)	4	(26.7)	54	(90.0)	80	(87.9)	138	(83.1)	46	(85.2)
Multiple	4	(50.0)	1	(6.7)	5	(8.3)	0	(0.0)	6	(3.6)	2	(3.7)
Ethnicity												
Hispanic Or Latino	5	(62.5)	2	(13.3)	11	(18.3)	4	(4.4)	17	(10.2)	5	(9.3)
Not Hispanic Or Latino	3	(37.5)	13	(86.7)	49	(81.7)	86	(94.5)	148	(89.2)	49	(90.7)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	1	(0.6)	0	(0.0)
Weight (kg)												
Participants with data	8		15		60		91		166		54	
Mean	2.7		9.5		27.4		59.7		43.5		41.0	
SD	0.81		1.73		11.65		17.34		23.62		19.77	
Median	2.8		9.2		26.1		57.0		42.5		41.0	
Range	1.4 to 3.8		6.0 to 12.0		10.0 to 59.0		27.6 to 126.3		6.0 to 126.3		8.0 to 96.0	
Body Mass Index (kg/m²)												
Participants with data	8		15		60		91		166		54	
Mean	11.45		18.81		17.34		21.90		19.97		18.94	
SD	2.513		3.203		3.696		4.842		4.820		4.190	
Median	11.63		18.90		17.30		20.81		19.26		18.82	
Range	8.03 to 16.49		13.69 to 24.79		10.65 to 27.04		14.27 to 44.96		10.65 to 44.96		9.91 to 32.83	
Geographic Region												
North America	0	(0.0)	0	(0.0)	0	(0.0)	8	(8.8)	8	(4.8)	2	(3.7)
Europe, Middle East and Africa	3	(37.5)	13	(86.7)	50	(83.3)	83	(91.2)	146	(88.0)	49	(90.7)
Latin America	5	(62.5)	2	(13.3)	10	(16.7)	0	(0.0)	12	(7.2)	3	(5.6)

SD=Standard deviation.
Note: Age was derived in years with 3 decimals, from data collected in years and months when participants were randomized. For participants less than 3 months old the number of days postnatal were collected and the age were also derived in years. (Example: The age in years of a 7 day old were derived as 7/365 = 0.0191 years.)
Only participants from Groups 2-3 Cohort 2 were included in study PN014.

Participants were from birth to 17.0 years of age, and the mean age was comparable for the tedizolid and comparator groups (10.6 years vs 10.7 years).

Most participants had ABSSSI due to a gram-positive pathogen at baseline (220 participants 28 days to <18 years of age), while the neonatal participants (8 participants from birth to <28 days of age) were receiving treatment or prophylaxis for gram-positive infection (the majority had sepsis at baseline).

The CHMP noted that, overall, 154 participants <12 years of age received ≥1 dose of tedizolid phosphate in P013, P014, and P018. A total of 174 participants <18 years of age received ≥1 dose of

tedizolid phosphate in P012, P014, and P018 and were included in the safety data pool for the pooled multiple-dose paediatric studies.

The P013 study enrolled 32 patients aged from 2 to 12 years (all SD) and the P014 study included 47 patients: 14 patients aged from 28 days to <24 months and 31 patients from birth to < 28 days. Out of the patients included in P014, the number of patients to MD IV were only 8 (all aged from birth to <28 days: 4 full-term and 4 preterm neonates). In the Phase 3 study, MK-1986-018 (P018), a total of 100 patients were enrolled (75 tedizolid and 25 comparator), of those 20 patients aged 28 days to <2 years. Of note that no patient from birth to < 28 days was enrolled in this study.

All in all, although compliant with the PIP in terms of the number of the patients enrolled, the safety database is limited and limits the chance of detecting adverse events. However, as the extension of indication is mainly supported by PK data this is acceptable. Nevertheless, the limitations found in the PK analysis for this population (especially for the MD regimen where data from 4 neonates with implausible PK profile could not be used in the popPK analysis) and the very low number of neonates enrolled (n=16 full-term; 4 of those MD IV and n=17 pre-term; 4 of those MD IV) raise concerns and do not allow drawing firm conclusions regarding the safety profile in this extremely vulnerable population. The MAH was invited to discuss the safety of tedizolid in this extreme vulnerable population (from birth to < 28 days) and propose pharmacovigilance activities, if appropriate.

The MAH confirmed that the observed concentrations on the 4 excluded neonates (1 preterm and 3 full term) were not biologically plausible and significantly deteriorated the performance of the PopPK model. Examination of the demographics and the study records, including dose preparation and administration, did not offer a clear explanation for the observations in the 4 neonates, and thus, it is only based on the plasma levels that the exclusions are supported. In fact, these concentrations are, indeed, implausible, as they are several orders of magnitude lower compared to all remaining participant data, including other neonatal data. Although a logical explanation for these outlier data is not possible to be found, its exclusion is supported.

Since the number of subjects with multiple dose administrations was very low (3 neonates) the risk existed that the model was not able to describe them appropriately. However, the individual plots of the Population and individual predicted tedizolid concentrations seem to pick well the observed data, and the pcVPC plots of the preterm and full-term neonates do also seem to be well characterized, although some underprediction in pre-term subjects was observed.

Taking in consideration that tedizolid shows linear and time-invariant kinetics, that there was a good characterization of the PK in single dose, the expected accumulation is not high and the available multiple-dose profiles do not show a significant departure from the expected behaviour, it was agreed that the current population PK model is appropriately characterizing the PK in the neonatal population, and the issue was considered to be resolved.

Adverse events

For the Summary of Clinical Safety submitted with this application, the MAH performed an up-versioning from the different MedDRA versions originally used for coding AEs in the CSRs to the most current MedDRA version (26.0) for coding AEs in the integrated AE data pool across the multiple-dose studies. No clinically important differences in the coding of AEs and no changes in safety conclusions were noted with this up-versioning.

Summary Analysis of Adverse Events

Individual Studies (P013, P014, P018)

No clinically meaningful differences in percentages of participants with AEs were observed for any AE category by age group in P013, P014, and P018 or by treatment group in P018.

Overall, the percentage of participants with AEs was low (28.1% of participants in P013, 17.0% of participants in P014, and 27.0% of participants in P018), and was comparable for the tedizolid and comparator groups (28.0% vs 24.0%) in P018.

The majority of AEs were mild in each study.

The percentage of participants with AEs was generally comparable across age groups in each study.

No trends in percentages of participants with AEs were observed based on route (IV or oral) or frequency (single- or multiple-dose) of administration.

No trends in percentages of participants with AEs were observed by SOC or PT.

The percentage of participants with drug-related AEs was low (<10% of participants) in P013, P014, and P018, and was comparable for the tedizolid and comparator groups (9.3% vs 8.0%) in P018.

Two SAEs were reported for 2 participants, 1 (appendicitis) in P013 and 1 (therapeutic product effect incomplete) in P014; neither event was considered to be related to study intervention by the investigator. No SAEs were reported in P018.

No deaths were reported and no participant discontinued study intervention due to an AE.

Pooled Multiple-Dose Studies (P012, P014, P018)

The percentage of participants with AEs was generally comparable across age groups and treatment groups in the pooled multiple-dose studies, consistent with results from the individual studies.

Table 2.7.4-absssichild: 3
Adverse Event Summary
Pediatric (Pooled PN012, PN014, and PN018) Studies with Multiple Doses of Study Medication
Safety Analysis Set

	0 to <28 days Tedizolid		28 days to <2 years Tedizolid		2 to <12 years Tedizolid		12 to <18 years Tedizolid		28 days to <18 years Tedizolid		28 days to <18 years Comparator	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		15		60		91		166		54	
with one or more adverse events	2	(25.0)	7	(46.7)	14	(23.3)	13	(14.3)	34	(20.5)	9	(16.7)
with no adverse event	6	(75.0)	8	(53.3)	46	(76.7)	78	(85.7)	132	(79.5)	45	(83.3)
with drug-related[a] adverse events	0	(0.0)	1	(6.7)	6	(10.0)	3	(3.3)	10	(6.0)	3	(5.6)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	1	(0.6)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	1	(0.6)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	1	(0.6)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.
The drug-related adverse event indicates related to study drug.
Discontinued drug refers to an AE leading to study medication withdrawn.
Note: Only treatment-emergent AEs are presented in this table. Only participants from Groups 2-3 Cohort 2 were included in study PN014.

Source: [ISS: adam-adsl; adae]

The percentage of participants with AEs was comparable for the tedizolid and comparator groups (20.5% vs 16.7%) across the pooled comparator-controlled studies, consistent with the results from the individual comparator-controlled study P018.

No trends in percentages of participants with AEs were observed by SOC or PT.

The percentage of participants with drug-related AEs was low (≤10% of participants) in each age group across the pooled multiple-dose studies, and was comparable for the tedizolid and comparator groups (6.0% vs 5.6%) across the pooled comparator-controlled studies.

Three SAEs were reported for 1 participant 12 to <18 years of age (tedizolid group, P012); the events were considered by the investigator to be not related to study intervention.

Common Adverse Events

Most Frequent Adverse Events

Individual Studies (P013, P014, P018)

No trends in percentages of participants with AEs were observed by SOC or by PT for any age group or treatment group in P013, P014, and P018.

In P013, the most frequently reported AEs (≥5% of participants overall) were pyrexia (3/32, 9.4%), vomiting (3/32, 9.4%), headache (2/32, 6.3%), haemoglobin decreased (2/32, 6.3%), and nausea (2/32, 6.3%).

Among the AEs reported, there was no PT that was reported for ≥5% of participants in P014.

In P018, the most frequently reported AEs (≥5% of participants in a treatment group) were diarrhoea (3/25, 12.0%) and decreased appetite (2/25, 8.0%) in the comparator group (no AE was reported for ≥5% of participants in the tedizolid group).

Pooled Multiple-Dose Studies (P012, P014, P018)

No trends in percentages of participants with AEs were observed by SOC or PT across age groups or treatment groups in the pooled multiple-dose studies, consistent with results from individual studies.

Drug-Related Adverse Events

Individual Studies (P013, P014, P018)

No trends in percentages of participants with drug-related AEs were observed for any age group or treatment group in P013, P014, and P018.

The percentage of participants with drug-related AEs was low (<10% of participants in any study or treatment group) in P013, P014, and P018, and was comparable for the tedizolid and comparator groups (9.3% vs 8.0%) in P018.

Drug-related AEs were reported for 3/32 (9.4%) participants in P013, 1/47 (2.1%) participant in P014, and 9/100 (9.0%) participants in P018 (tedizolid group: 7/75, 9.3%; comparator group: 2/25, 8.0%).

One drug-related AE (anaemia) in P013 was classified as an ECI.

All drug-related AEs were reported as mild.

Drug-related AEs reported for >1 participant in a study or treatment group were nausea (n=3; tedizolid group: 2, comparator group: 1) and phlebitis (n=2 in the tedizolid group), all in P018.

There were 2 AEs of phlebitis from the SMQ of Infusion Site Reactions, in 2 participants in the tedizolid group in P018. Both events were reported as mild and resolved, and both were considered by the investigator to be related to study intervention. The participants did not discontinue study intervention or from the study.

Pooled Multiple-Dose Studies (P012, P014, P018)

No trends in percentages of participants with drug-related AEs were observed across age groups or treatment groups in the pooled multiple-dose studies [Table below], consistent with results from the individual studies.

The percentage of participants with drug-related AEs was low (≤10%) across age groups from 28 days to <18 years of age and was comparable for the tedizolid and comparator groups across the pooled comparator-controlled studies.

No drug-related AEs were reported for neonatal participants (from birth to <28 days of age) in multiple-dose cohorts.

Table 2.7.4-absssichild: 4
Participants With Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Incidence > 0% in One or More Treatment Groups)
Pediatric (Pooled PN012, PN014, and PN018) Studies with Multiple Dose of Study Medication
Safety Analysis Set

	0 to <28 days Tedizolid		28 days to <2 years Tedizolid		2 to <12 years Tedizolid		12 to <18 years Tedizolid		28 days to <18 years Tedizolid		28 days to <18 years Comparator	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		15		60		91		166		54	
with one or more related treatment-emergent adverse events	0	(0.0)	1	(6.7)	6	(10.0)	3	(3.3)	10	(6.0)	3	(5.6)
with no related treatment-emergent adverse events	8	(100.0)	14	(93.3)	54	(90.0)	88	(96.7)	156	(94.0)	51	(94.4)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(6.7)**	**3**	**(5.0)**	**0**	**(0.0)**	**4**	**(2.4)**	**2**	**(3.7)**
Diarrhoea	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	1	(0.6)	0	(0.0)
Nausea	0	(0.0)	0	(0.0)	2	(3.3)	0	(0.0)	2	(1.2)	2	(3.7)
Vomiting	0	(0.0)	1	(6.7)	1	(1.7)	0	(0.0)	2	(1.2)	0	(0.0)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(3.3)**	**3**	**(1.8)**	**0**	**(0.0)**
Alanine aminotransferase increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	1	(0.6)	0	(0.0)
Aspartate aminotransferase increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	1	(0.6)	0	(0.0)
Liver function test increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	1	(0.6)	0	(0.0)
Metabolism and nutrition disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.9)**
Decreased appetite	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.7)**	**0**	**(0.0)**	**1**	**(0.6)**	**0**	**(0.0)**
Rash erythematous	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	1	(0.6)	0	(0.0)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(3.3)**	**0**	**(0.0)**	**2**	**(1.2)**	**0**	**(0.0)**
Phlebitis	0	(0.0)	0	(0.0)	2	(3.3)	0	(0.0)	2	(1.2)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Determined by the investigator to be related to the drug.
Only participants from Groups 2-3 Cohort 2 were included in study PN014.

Source: [ISS: adam-adsl; adae]

Analysis of Adverse Events by Organ System or Syndrome (Others Adverse Events of Interest)

Individual Studies (P013, P014, P018)

Haematopoietic Cytopenia AEs

There was no pattern of AEs to indicate myelosuppression in P013, P014, and P018.

In P018, prespecified Tier 1 AEs included the SMQ hematopoietic cytopenias, which were observed as follows in the 3 studies:

There were 3 AEs (1 anaemia, 2 haemoglobin decreased) in P013 and 1 AE (anaemia) in P014 from the SMQ of hematopoietic cytopenias. The 2 anaemia AEs (1 in P013 and 1 in P014) met the definition of ECIs, while the 2 AEs of haemoglobin decreased (both in P013) did not. All 4 events were reported as mild or moderate and resolved. The investigator considered the anaemia event and 1 event of haemoglobin decreased in P013 to be related to study intervention; the Sponsor assessed the anaemia event to be likely related to blood loss during surgical procedures. The investigator considered the anaemia event in P014 to be not related to study intervention. None of the 4 events resulted in discontinuation of study intervention or from the study.

There were 2 AEs (1 of thrombocytopenia; 1 of neutropenia) from the SMQ of hematopoietic cytopenias in the tedizolid group in P018. The thrombocytopenia event met the P018 study protocol definition of an ECI; the neutropenia event did not. Both events were reported as mild and resolved without treatment; the events were considered by the investigator to be not related to study intervention. Neither participant discontinued study intervention or discontinued from the study.

Pooled Multiple-Dose Studies (P012, P014, P018)

No trends in AEs of interest were observed by age group or treatment group across the pooled multiple dose studies, consistent with results from the individual studies.

Serious adverse event/deaths/other significant events

Deaths

There were no deaths due to any cause reported in P012, P013, P014, and P018.

Serious Adverse Events

Individual Studies (P013, P014, P018)

No trends in percentages of participants with SAEs were observed in P013, P014, and P018.

Two SAEs were reported for 2 participants, 1 (appendicitis) in P013 and 1 (therapeutic product effect incomplete) in P014; both events were reported as resolved and were considered by the investigator to be not related to study intervention.

No SAEs were reported for participants in P018.

Pooled Multiple-Dose Studies (P012, P014, P018)

No trends in percentages of participants with SAEs were observed in the pooled multiple-dose studies consistent with results from the individual studies.

Three SAEs (pneumonia, sepsis, and venous thrombosis limb) were reported for 1 participant 12 to <18 years of age (tedizolid group, P012); the events led to discontinuation from study intervention and from the study and were considered by the investigator to be not related to study intervention.

No SAEs were reported for participants <12 years of age in the multiple-dose studies.

Drug Serious Adverse Events

No drug-related SAEs were reported for participants in P012, P013, P014, and P018.

Other Significant Adverse Events

Individual Studies (P013, P014, P018)

Three event of clinical interest (ECIs) were reported for 3 participants, 1 (anaemia) in P013, 1 (anaemia) in P014, and 1 (thrombocytopenia) in the tedizolid group in P018.

An AE of anaemia was reported for 1 participant 2 to <6 years of age in P013. The event was assessed as moderate in severity and was reported as resolved. The investigator considered the event to be related to study intervention. The Sponsor assessed the event to be likely related to blood loss during surgical procedures undergone on the same day of onset as the AE.

An AE of anaemia was reported for 1 participant, a preterm neonate <28 days of age, in P014. The event was assessed as mild in severity and was reported as resolved. The investigator considered the event to be not related to study intervention.

An AE of thrombocytopenia was reported for 1 participant 28 days to <2 years of age in the tedizolid group in P018. The event was assessed as mild in severity and was reported as resolved. The investigator considered the event to be not related to study intervention.

Pooled Multiple-Dose Studies (P012, P014, P018)

ECIs were not pooled across studies due to differences in study design (ECIs were not prespecified in the study protocol for P012).

The Committee considered that, overall, the percentage of participants with AEs was low (28.1% of participants in P013, 17.0% of participants in P014, and 27.0% of participants in P018), and was comparable for the tedizolid and comparator groups (28.0% vs 24.0%) in P018. The majority of AEs were mild and no clinically meaningful differences in percentages of participants with AEs were observed for any AE category by age group in P013, P014, and P018 or by treatment group in P018.

Two SAEs were reported for two participants but neither event was considered to be related to study intervention by the investigator, which is agreed. No deaths were reported, and there were no discontinuations or interruptions of study intervention due to AEs in P013, P014, or P018. From the data available, no new safety adverse event findings emerged.

Laboratory findings

Haematology

Evaluation of Changes in Haematology

There was no indication of myelosuppression in single- or multiple-dose studies across age groups in any individual study or in the pooled population in participants <18 years of age.

Individual Studies (P013, P014, P018)

No clinically meaningful differences were observed between mean values at baseline and post-dose assessments for any haematology parameter in P013 or P014.

Mean changes from baseline to post-dose in laboratory values for haematology were comparable for the tedizolid and comparator groups in P018. Comparable percentages of participants in each treatment group had changes in most categories (low/normal/high) between baseline and the EOT visit for

haematology. Notably, no indication of myelosuppression was observed in either treatment group in P018.

Key observations from evaluation of changes in haematology laboratory values in each study were as follows:

In P013, 1 participant had a decrease in haemoglobin from baseline to post-dose (Day 2) that the investigator considered to be an AE (anaemia) that also met the criteria for an ECI.

In P014, shifts in haemoglobin were more frequently observed in comparison with other haematology parameters, particularly in neonates.

- All 6 neonatal participants who had a Grade 1 or Grade 2 decrease in haemoglobin from baseline to post-dose in P014 had concurrent sepsis or prior surgery. Of these, 1 neonatal participant had a decrease in haemoglobin that was considered by the investigator to be a clinically significant hematologic AE (anaemia), and, therefore, an ECI; the investigator considered the event to be not related to study intervention.
- One participant (6 to <24 months of age in a single-dose IV cohort) in P014 had a shift from a normal baseline haemoglobin value to Grade 3 post-dose that was considered by the investigator to be due to an operative intervention and not clinically meaningful.

In P018, the overall percentage of participants reporting post-baseline observations meeting the DAIDS v.2.1 criteria for Grade 3 or Grade 4 toxicity was low (≤4%) for haematology parameters in both treatment groups and across age groups.

Pooled Multiple-Dose Studies (P012, P014, P018)

No trends in haematology changes were observed by age group or treatment group in the pooled multiple dose studies, consistent with observations from the individual studies.

Two participants receiving tedizolid phosphate had a change of ≥3 grades from baseline to the worst observed post-dose grade in haematology values.

- One participant 28 days to <2 years of age in P018 had a change from Grade 0 at baseline to Grade 4 post-dose in platelets that was reported as an ECI (thrombocytopenia). The investigator assessed the event as mild in severity and the event was reported resolved. The investigator considered the event to be not related to study intervention.
- One participant, a preterm neonate <28 days of age in P014 had a Grade 1 to Grade 4 toxicity grade change in haemoglobin that was reported as an ECI (anaemia). The investigator assessed the event as mild in severity and the event was reported resolved. The investigator considered the event to be not related to study intervention.

One participant 28 days to <18 years of age receiving comparator in P012 had a change from Grade 0 at baseline to Grade 3 post-dose in haemoglobin (as reported in the CSR previously submitted for P012). The investigator did not consider the change to be an AE (ECIs were not prespecified for P012).

Potentially Clinically Significant Low Haematology Values

Pooled Multiple-dose Studies (P012, P014, P018)

Post-dose PCS low laboratory values for haemoglobin, platelets, and neutrophils were defined as values that were <75% of LLN (or <50% of LLN for absolute neutrophil count) (Table below). Few PCS low haematology values were observed in the pooled population, with no trends observed by age group. The

percentage of participants with PCS low haematology values was comparable for the tedizolid and comparator groups for participants (28 days to <18 years of age) in the comparator-controlled studies.

Exposure-Response Analysis

An exploratory analysis of PCS low haematology laboratory values by tedizolid exposure was performed. Over the tedizolid exposure ranges in the pooled multiple-dose studies, no association was observed between PCS low haematology laboratory values and tedizolid exposures.

Table 2.7.4-absssichild: 5
Participants with Potentially Significant Lowest Hematology Laboratory Values
Pediatric (Pooled PN012, PN014, and PN018) Studies with Multiple Doses of Study Medication
Safety Analysis Set

		0 to <28 days		28 days to <2 years		2 to <12 years		12 to <18 years		28 days to <18 years		28 days to <18 years	
		Tedizolid		Tedizolid		Tedizolid		Tedizolid		Tedizolid		Comparator	
Test Name (Unit)	Criterion	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
Absolute Neutrophil Count (10^9/L)	<50% of lower limit of normal (LLN)	0/8	0.0	0/14	0.0	0/57	0.0	4/85	4.7	4/156	2.6	1/51	2.0
Hemoglobin (g/L)	<75% of lower limit of normal (LLN)	0/8	0.0	0/14	0.0	0/58	0.0	1/85	1.2	1/157	0.6	1/51	2.0
Platelets (10^9/L)	<75% of lower limit of normal (LLN)	0/8	0.0	1/14	7.1	4/58	6.9	1/82	1.2	6/154	3.9	1/51	2.0

n: Number of participants with postbaseline test results that met the predetermined criterion.
m: Participants with at least one post-baseline test result that are within two days after the last dose of active drug.
Potentially significant lowest values: <75% (<50% for absolute neutrophil count) of lower limit of normal (LLN) for post-baseline measurements.
Laboratory values on or after the first dose and within two days after the last dose of active drug are summarized.
Only participants from Groups 2-3 Cohort 2 were included in study PN014.

Source: [ISS: adam-adlb]

Chemistry

Evaluation of Changes in Chemistry

Individual Studies (P013, P014, P018)

No clinically meaningful differences were observed between mean values at baseline and the post-dose assessment for any clinical chemistry parameter in P013 and P014.

Mean changes from baseline to post-dose in laboratory values for clinical chemistry were comparable for the tedizolid and comparator groups in P018. Comparable percentages of participants in each treatment group had changes in most categories (low/normal/high) between baseline and the EOT visit for clinical chemistry.

Key observations from evaluation of changes in clinical chemistry laboratory values in each study were as follows:

The overall percentage of participants with post-baseline observations meeting the DAIDS v.2.1 criteria for Grade 3 or Grade 4 toxicity was low (≤4%) in both groups in P018 for most clinical chemistry parameters, except creatinine.

For creatinine, in the tedizolid group, 10 of 70 (14.3%) participants had a Grade 3 shift between baseline and EOT and no participants had a Grade 4 shift. In the comparator group, no participants had a Grade 3 shift between baseline and EOT and 4 of 23 (17.4%) participants had a Grade 4 shift. None of the creatinine changes in P018 were considered clinically significant by the investigators.

Pooled Multiple-Dose Studies (P012, P014, P018)

Other than the creatinine observations noted above, few shifts of ≥3 grades from baseline to the worst post-baseline value were observed for any chemistry parameter, and none were reported in participants <12 years of age.

Vital signs, physical findings, and other observations related to safety

Individual Studies (P013, P014, P018)

No clinically meaningful changes in mean values over time were observed after IV and/or oral dosing for any vital sign in any age group in P013, P014, and P018. Overall, vital signs were comparable for the tedizolid and comparator groups over time in P018.

Neurological Findings

No neurological AEs were reported for any participant in P013, P014, and P018.

Visual Acuity Scores

No visual acuity AEs were reported for any participant in P013 and P014. A single AE of reduced visual acuity was reported for 1 participant in the tedizolid group in P018; the event was reported as mild in intensity and was concurrent with an AE of allergic conjunctivitis that was reported as moderate in intensity. Both events resolved within 3 weeks of the onset of the reduced visual acuity AE and were considered by the investigator to be not related to study intervention.

Pooled Multiple-dose Studies (P012, P014, P018)

Time points for vital signs assessments were not aligned across studies; therefore, pooled analysis for specific time points was not applicable.

Overall, the Committee considered that no new emergent safety signals with regard to laboratory findings or vital signs were observed. With regards to the evaluation of changes in haematology, from the limited database available, there was no indication of myelosuppression (which is an important identified risk in the RMP) in single- or multiple-dose studies across age groups in any individual study or in the pooled population in participants <18 years of age.

Safety in special populations

Intrinsic Factors

No clinically meaningful differences between age groups in percentage of patients with AEs were observed for any AE category in P013, P014, and P018. Evaluations of safety by intrinsic factors other than age were not performed for P013, P014, or P018.

Extrinsic Factors

Evaluations of the safety of tedizolid phosphate by extrinsic factors were not performed for P013, P014, or P018.

Use in Pregnancy and Lactation

Pregnancy was an exclusion in P013 and P018 and was not applicable in P014. Therefore, there are no new clinical data to further inform the risk assessment for the use of tedizolid phosphate during pregnancy and lactation.

Overdose

No cases of overdose were reported in P013, P014, and P018; therefore, no new information is available to change characterization of risks for overdose or new data to support additional recommendations regarding the management of overdose.

Drug Abuse

The drug abuse and dependence potential of tedizolid phosphate has not been characterized. Based on the mechanism of action, tedizolid phosphate is unlikely to have abuse potential.

Withdrawal and Rebound

Based on the cumulative data in the clinical development program, no safety signal has been identified that would suggest a potential for withdrawal or rebound effects after discontinuing tedizolid phosphate.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Based on the cumulative data in the clinical development program, no safety signal has been identified that would suggest any effects on the ability to drive or operate machinery or impairment of mental ability with tedizolid phosphate.

Safety related to drug-drug interactions and other interactions

DDIs were not specifically evaluated in P013, P014, or P018. No new DDI studies were conducted for the paediatric indication.

Discontinuation due to adverse events

Adverse Events Leading to Discontinuation of Study Intervention

Individual Studies (P013, P014, P018)

There were no discontinuations of study intervention due to AEs in P013, P014, and P018.

Pooled Multiple-dose Studies (P012, P014, P018)

One participant 12 to <18 years of age (tedizolid group, P012) discontinued study intervention and discontinued the study due to 3 SAEs; the events were considered by the investigator to be not related to study intervention.

Adverse Events Leading to Intervention Interruption

There were no interruptions of study intervention due to AEs in P012, P013, P014, and P018 (other than the one participant's discontinuation of study intervention due to SAEs in P012.

The CHMP acknowledged that there were no discontinuations or interruptions of study intervention due to AEs in P013, P014, or P018.

Post marketing experience

Tedizolid phosphate was first approved in the United States on 20-JUN-2014 (IBD) and has been approved for use in adults in 42 countries as of 31-DEC-2023. There are no records of any registration being revoked or withdrawn for safety reasons. A review of cumulative post marketing AEs was conducted from market introduction (20-JUN-2014) through 31-DEC-2023 and did not identify any new safety issues. Results of the analysis of available post marketing data from adult and adolescent patients are consistent with the known safety profile of tedizolid phosphate.

Post marketing Patient Exposure

Patient exposure estimates from 20-JUN-2016 to 31-DEC-2023 were calculated from the Company's internal distribution data from the WFRS and FSA database. The total cumulative patient exposure is approximately 447,086 patient years of treatment with tedizolid phosphate. This estimation was based on the assumption that patients received either 6 days of IV or 6 days of oral administration (ie, there was no IV to oral switch).

Post marketing Adverse Events

Overall, 415 SAEs have been reported in a total of 246 reports from spontaneous, noninterventional studies and other sources, from the IBD (20-JUN-2014) through 31-DEC-2023 . Of the 246 reports, 209 (84.9%) were spontaneous, 12 (4.8%) were from noninterventional studies, and 25 (10.1%) were other. The patient's age was provided in 168 reports and ranged from 12 to 98 years of age; 163 were adult patients and 5 were adolescent patients (12 to <18 years of age), there are no reports in children <12 years of age.

Table 2.7.4-absssichild: 6
SOC for Postmarketing SAEs Reported for Tedizolid Phosphate
From 20-JUN-2014 to 31-DEC-2023

SOC	Number of Serious Events	Percentage Serious Events
Blood and lymphatic system disorders	79	19.04%
Infections and infestations	57	13.73%
General disorders and administration site conditions	49	11.81%
Nervous system disorders	35	8.43%
Gastrointestinal disorders	31	7.47%
Investigations	26	6.27%
Skin and subcutaneous tissue disorders	18	4.34%
Renal and urinary disorders	15	3.61%
Hepatobiliary disorders	14	3.37%
Metabolism and nutrition disorders	14	3.37%
Respiratory, thoracic and mediastinal disorders	12	2.89%
Surgical and medical procedures	11	2.65%
Injury, poisoning and procedural complications	10	2.41%
Cardiac disorders	9	2.17%
Eye disorders	7	1.69%
Immune system disorders	7	1.69%
Vascular disorders	7	1.69%
Musculoskeletal and connective tissue disorders	6	1.45%
Psychiatric disorders	5	1.20%
Ear and labyrinth disorders	2	0.48%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.24%
Total	415	100.00%
SAE=serious adverse event; SOC=System Organ Class		

The SOCs with the most frequently reported SAEs were Blood and lymphatic system disorders (79 events), Infections and infestations (57 events), and General disorders and administration site conditions (49 events).

The 3 most frequently reported PTs in the blood and lymphatic system disorders SOC were thrombocytopenia (42), anaemia (13), and pancytopenia (7), that are labelled terms for tedizolid phosphate. Review of the events did not identify any new safety concerns.

The 3 most frequently reported PTs in the infections and infestations SOC were cellulitis (8), staphylococcal infection (6), and pneumonia (5). Review of the events did not identify any new safety concerns.

The 3 most frequently reported PTs in the General disorders and administration site conditions SOC were death (16), drug ineffective (13), and adverse event (10). Review of the reports did not identify any new safety concerns.

In summary, a cumulative analysis of post marketing SAEs as of 31-DEC-2023 did not identify new safety issues for tedizolid phosphate. The safety profile of tedizolid phosphate is adequately described in the product labelling. The overall benefit-risk for tedizolid phosphate continues to be positive. The MAH will continue to monitor the safety of tedizolid phosphate through routine pharmacovigilance processes.

Worldwide Literature Search

All published clinical literature on tedizolid phosphate was reviewed for consistency with the safety findings reported within this extension of indications application.

The CHMP acknowledged that the MAH stated that a review of cumulative post marketing AEs was conducted from market introduction through December 2023 and did not identify any new safety issues. The post marketing exposure predominantly reflects use in adults. There are no reports of post marketing AEs in children <12 years of age.

2.5.1. Discussion on clinical safety

Tedizolid is currently approved to be administered in adults and adolescents ≥12 years of age with ABSSSI. With this type II variation, the MAH intends to extend the approved indication to the paediatric population from birth to <12 years of age. The development program for the paediatric population <12 years of age included 3 clinical studies (2 Phase 1 and 1 Phase 3).

The 2 Phase 1 studies, MK-1986-013 (P013) and MK-1986-014 (P014), evaluated the PK, safety, and tolerability of a single oral or IV dose of tedizolid phosphate in participants 2 to <12 years of age (P013) and from birth to <2 years of age (P014). P014 also included multiple-dose neonatal (full-term and preterm neonates from birth to <28 days of age) cohorts to evaluate the PK, safety, and tolerability of multiple IV doses of tedizolid phosphate in the neonatal age group. In P014 study, no MD regimen was evaluated for patients aged 28 days to <24 months. The Phase 3 study, MK-1986-018 (P018), evaluated the safety and efficacy of multiple IV and oral doses of tedizolid phosphate in participants <12 years of age. In this study, a total of 100 patients were enrolled (75 tedizolid and 25 comparator), of those 20 patients aged 28 days to <2 years. Of note that no patient from birth to < 28 days was enrolled in this phase 3 study.

Safety results from P013, P014, and P018 were presented by individual study. Additionally, safety results from the multiple-dose cohorts of P014 and from P018 were pooled with safety results from a multiple-dose Phase 3 study MK-1986-012 (P012, previously submitted as part of a prior application to support

an extension of indication to the adolescent population) in adolescents 12 to <18 years of age with ABSSSI, which is considered acceptable.

Overall, 154 participants <12 years of age received ≥1 dose of tedizolid phosphate in P013, P014, and P018, and 25 received ≥1 dose of comparator in P018. A total of 174 participants <18 years of age received ≥1 dose of tedizolid phosphate in P012, P014, and P018 and were included in the safety data pool for the pooled multiple-dose paediatric studies.

The P013 study enrolled 32 patients aged from 2 to 12 years (all SD) and the P014 study included 47 patients: 14 patients aged from 28 days to <24 months and 33 patients from birth to < 28 days. Out of the patients included in P014, the number of patients to MD IV were only 8 (all aged from birth to <28 days: 4 full-term and 4 preterm neonates). In the Phase 3 study, MK-1986-018 (P018), a total of 100 patients were enrolled (75 tedizolid and 25 comparator), of those 20 patients aged 28 days to <2 years. No patient from birth to < 28 days was enrolled in this study.

At baseline, most participants had ABSSSI due to a gram-positive pathogen (220 participants 28 days to <18 years of age), while the neonatal participants (8 participants from birth to <28 days of age) were receiving treatment or prophylaxis for gram-positive infection (the majority had sepsis).

Although compliant with the PIP in terms of the number of the patients enrolled, the safety database is considered to be limited and limits the chance of detecting adverse events. However, as the extension of indication is mainly supported by PK data this is acceptable. Nevertheless, the limitations found in the PK analysis for participants <28 days (particularly for the MD regimen where data from 4 neonates with implausible PK profile could not be used in the popPK analysis) and the very low number of neonates (n=16 full-term; 4 of those MD IV and n=17 preterm; 4 of those MD IV) raise concerns and do not allow drawing firm conclusions regarding the safety profile in this extremely vulnerable population. The MAH was invited to discuss the safety of tedizolid in this extreme vulnerable population (from birth to < 28 days) and propose pharmacovigilance activities if appropriate.

The MAH confirmed that the observed concentrations on the 4 excluded neonates (1 preterm and 3 full term) were not biologically plausible and significantly deteriorated the performance of the PopPK model. Examination of the demographics and the study records, including dose preparation and administration, did not offer a clear explanation for the observations in the 4 neonates, and thus, it is only based on the plasma levels that the exclusions are supported. In fact, these concentrations are, indeed, implausible, as they are several orders of magnitude lower compared to all remaining participant data, including other neonatal data. Although a logical explanation for these outlier data is not possible to be found, its exclusion was supported.

Taking in consideration that tedizolid shows linear and time-invariant kinetics, that there was a good characterization of the PK in single dose, the expected accumulation is not high and the available multiple-dose profiles do not show a significant departure from the expected behaviour, it is agreed that the current population PK model is appropriately characterizing the PK in the neonatal population.

Overall, the percentage of participants with AEs was low (28.1% of participants in P013, 17.0% of participants in P014, and 27.0% of participants in P018), and was comparable for the tedizolid and comparator groups (28.0% vs 24.0%) in P018. The majority of AEs were mild and no clinically meaningful differences in percentages of participants with AEs were observed for any AE category by age group in P013, P014, and P018 or by treatment group in P018. In P013, the most frequently reported AEs (≥5% of participants overall) were pyrexia (3/32, 9.4%), vomiting (3/32, 9.4%), headache (2/32, 6.3%), haemoglobin decreased (2/32, 6.3%), and nausea (2/32, 6.3%). Among the AEs reported, there was no PT that was reported for ≥5% of participants in P014. In P018, the most frequently reported AEs (≥5% of participants in a treatment group) were diarrhoea (3/25, 12.0%) and decreased appetite (2/25, 8.0%) in the comparator group (no AE was reported for ≥5% of participants in the tedizolid group). The

percentage of participants with drug-related AEs was low (<10% of participants in any study or treatment group) in P013, P014, and P018, and was comparable for the tedizolid and comparator groups (9.3% vs 8.0%) in P018. In the pooled multi-dose studies, no trends in percentages of participants with drug-related AEs were observed across age groups or treatment groups.

Two SAEs were reported for two participants and neither event was considered to be related to study intervention by the investigator, which is agreed. No deaths were reported, and there were no discontinuations or interruptions of study intervention due to AEs in P013, P014, or P018. From the data available, no new safety adverse event data have emerged from these studies.

No new emergent safety signals with regard to laboratory findings or vital signs were observed. In what concerns to the evaluation of changes in haematology, from the limited database available, there was no indication of myelosuppression (which is an important identified risk in the RMP) in single- or multiple-dose studies across age groups in any individual study or in the pooled population in participants <18 years of age.

During the assessment, the MAH was requested to clarify if tablet acceptability had been assessed in children (2 to less than 12 years old). The MAH stated that no tablet acceptability was assessed in children aged 2 to less than 12 years. Even though most children <12 years will require weight-based dosing, it was however possible that children of sufficient weight are eligible to receive 200 mg once daily dosing. As stated by the MAH, IV formulation would be the only available route of administration if these children cannot swallow a tablet, which should be discussed with the HCP. In addition, in order to assess the risk of chocking the MAH performed a search in the global safety database to identify any report of choking with tablets. No cases were found for the PT Choking.

2.5.2. Conclusions on clinical safety

Taking in consideration that tedizolid shows linear and time-invariant kinetics, that there was a good characterization of the PK in single dose, the expected accumulation is not high and the available multiple-dose profiles do not show a significant departure from the expected behaviour, it was agreed that the current population PK model is appropriately characterizing the PK in the neonatal population.

Overall, the paediatric clinical development program for tedizolid has demonstrated an acceptable safety and tolerability profile, and no new safety signals were identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version (version 7.1) with this application. The (main) proposed RMP changes were the following:

- Submission of the extension of indication to include paediatric patients.
- Updated per EMA GVP Module V (Rev.2) RMP template guidance to remove "Myelosuppression", as important identified risk; "Peripheral and Optic nerve toxicity" and "Lactic acidosis" as important potential risks; and the safety concerns for missing information of "Treatment of acute bacterial skin and skin structure infections (ABSSSI) in severely immunocompromised patients (eg, patients with

neutropenia, transplant recipients, HIV/AIDS)" and "Treatment of ABSSSI in patient populations/conditions that were under-represented in pivotal studies (eg, elderly patients, diabetic patients, and patients with acute polymicrobial infections such as major abscesses or traumatic wounds) and potential need for longer course of treatment and/or adjunctive gram-negative antimicrobial therapy."

- Missing information of "Prolonged treatment >7 days" has been removed based on the completion of Merck Investigator Studies Programs (MISPs).

The main changes were:

Part I: Product overview

This section has been updated to incorporate administrative changes related to the description of the new proposed paediatric indication and new proposed dosage.

Proposed: Sivextro powder for concentrate for solution for infusion: Sivextro is indicated for the treatment of acute bacterial skin and soft structure infections (ABSSSI) in adult and paediatric patients. Sivextro film-coated tablets: Sivextro film-coated tablets are indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult patients and paediatric patients weighing at least 35 kg.

In addition, the dosage was also updated to separate the dose recommended to paediatric patients weighting at least 35 kg and paediatric patients less than 35 kg. A table with the recommended dose splitting by the weight band is included.

Part II: Safety specification

- **Module SI. Epidemiology of the indications and target population**

Epidemiology information has been updated. The new information concerns to incidence of soft tissue infections (SSTI's), overall and in paediatric population, as well as incidence of Methicillin-resistant *Staphylococcus aureus (MRSA)* infections. In addition, the prevalence of MRSA in Europe, overall and in paediatric patients, is included.

- **Module SIII. Clinical trial exposure**

The information concerning clinical trials has been updated to include the results of P013, P014 and P018. Studies P014 and P018 were the studies 6 and 9 of the approved Paediatric Investigation Plan.

In addition, patient exposure data from clinical studies was updated to include paediatric data. Table SIII.5 and table SIII.6 have been updated to include dose < 200 mg. Tables SIII.7, SIII.8 and SIII. 9 have been updated to include patients < 12 years.

- **Module SIV. Populations not studied in clinical trials**

Paediatric population data has been updated. The information regarding children has been removed from this section. Table SIV.4.1 regarding Safety concerns due to limitations of the clinical trial program has

been updated to include data regarding paediatric study P018 and to indicate that Prolonged treatment>7 days is no longer an outstanding concern.

- **Module SV. Post-authorization experience**

Post-authorization exposure has been updated to include the cumulative exposure from product launch up to 31 Dec 2023 including 447,086 estimated patient courses of treatment.

- **Module SVII. Identified and potential risks**

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII.1.2.1 has been removed since all safety concerns have been deleted.

Not applicable.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Important Identified Risks that are being reclassified

Based upon EMA GVP Module V (Rev 2) guidance, "Myelosuppression", previously classified as important identified risk, is removed from the list of RMP risks. The language in the approved label adequately describes this risk; a review of the cumulative data on this topic has not revealed any new relevant information that would warrant follow-up through the RMP. The results of three MISPs conducted to evaluate the tolerability of tedizolid phosphate long-term use did not further characterize this risk. No additional pharmacovigilance activities are planned to further characterize. This risk will continue to be evaluated through routine pharmacovigilance activities.

Important Potential Risks that are being reclassified

Based upon EMA GVP Module V (Rev 2) guidance,_"Peripheral and Optic nerve toxicity" and "Lactic acidosis", previously classified as important potential risks, are removed from the list of RMP risks. The language in the approved label adequately describes these risks; a review of the cumulative data on these topics has not revealed any new relevant information that would warrant follow-up through the RMP. The results of three MISPs, conducted to evaluate the tolerability of tedizolid phosphate long-term use did not further characterize these risks. No additional pharmacovigilance activities are planned to further characterize them. These risks will continue to be evaluated through routine pharmacovigilance activities.

Revision and Reclassification of concerns identified as Missing Information

1. 'Prolonged treatment >7 days' previously classified as missing information is removed from the list of safety concerns.

Three MISPs, considered additional pharmacovigilance activities, were conducted to evaluate the tolerability of tedizolid phosphate long-term use:

- Senneville E, Dinh A, Ferry, T Et al. Tolerance of Prolonged Oral Tedizolid for Prosthetic Joint Infections: Results of a Multicentre Prospective Study. Antibiotics 2021, 10, 4. .

- Morrisette T, Molina KC, Da Silva B, et al. Real-World Use of Tedizolid Phosphate for 28 Days or More: A Case Series Describing Tolerability and Clinical Success. Open Forum Infect Dis. 2022 Jun; 9(6).
- Miller G, Flores E, Launer B, et al. Safety and tolerability of tedizolid as oral treatment for bone and joint infections. Microbiol Spectr. 2023 Sep 26.

With the completion of these three MISPs, it is considered that there is currently data on long-term use; therefore, "Prolonged treatment >7 days" is no longer considered missing information for tedizolid phosphate. No new safety issues were identified; no additional pharmacovigilance activities are planned to further characterize this risk. Routine risk minimization measures remain adequate for maintaining the positive benefit risk profile for the product use in the targeted indications.

2. Based upon EMA GVP Module V (Rev 2) guidance, "Treatment of ABSSSI in severely immunocompromised patients (eg, patients with neutropenia, transplant recipients, HIV/AIDS)" and "Treatment of ABSSSI in patient populations/conditions that were under-represented in pivotal studies (eg, elderly patients, diabetic patients, and patients with acute polymicrobial infections such as major abscesses or traumatic wounds) and potential need for longer course of treatment and/or adjunctive gram-negative antimicrobial therapy", previously classified as missing information are removed from the list of RMP risks. According to EMA GVP Module V (rev.2), the absence of data itself (e.g. exclusion of a population using a concomitant medicinal product from clinical studies) does not automatically constitute a safety concern . No additional pharmacovigilance activities are planned to further characterize them, and these risks will continue to be evaluated through routine pharmacovigilance activities.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

There are no identified or potential risks for tedizolid phosphate.

SVII.3.2 Presentation of the Missing Information

There is no missing information for tedizolid phosphate.

Part II: Module SVIII Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Considering the data in the safety specification, the safety concerns listed above are appropriate. However, there is a pending question regarding the safety of tedizolid in the extreme vulnerable population (from birth to < 28 days). Depending of the MAH's responses and the pharmacovigilance activities proposed this population may be considered in the RMP as missing information.

In addition, the following safety concerns should be followed in the PSURs, with special focus in paediatric patients:

- Important Potential Risks

- Peripheral and Optic nerve toxicity
- Lactic acidosis

- Missing Information
  - Treatment of immunocompromised patients
  - Prolonged treatment >7 days

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

The specific adverse reaction follow-up questionnaires concerning the following safety concerns have been retired:

- Hematology
- Lactic acidosis
- Peripheral Optic neuropathy
- Serotonin syndrome

Annex 4 has been updated accordingly to remove the questionnaires associated with these safety concerns, since each questionnaire should be associated with a safety concern.

• Other forms of routine pharmacovigilance activities:

Not applicable. A review of the safety concerns will be performed at each PSUR elaboration.

III.2 Additional Pharmacovigilance Activities

Not applicable. There are no ongoing or planned additional pharmacovigilance activities for tedizolid products.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Overall conclusions on the PhV Plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Safety concerns previously listed in the safety specifications in the RMP should be followed in the PSUR with special focus in paediatric patients. Although safety in children under 2 years of age, and specially safety in neonates should not be included as missing information in the RMP, it should be detailed in the PSUR as missing information. In addition, cases with chocking or swallowing difficulties in paediatric patients who took tablets should be closely monitored in the following PSURs.

Part V: Risk minimisation measures

V.1 Routine risk minimisation measures

Not applicable

V.2 Additional risk minimisation measures

Not applicable. No important identified risk, important potential risk and missing information are included in the safety concerns list (Part II: Module SVIII)

V.3 Summary of Risk Minimization Measures

Not applicable.

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Part VI: Elements for a public summary of the RMP

Part I has been updated to include pediatric indication regarding paediatric patients and to include changes to the dosing regimen for those paediatric patients.

In addition, part II has been updated to remove all the safety concerns to align with GVP Module V (Rev 2) RMP guidance. There are no important identified or potential risks for Sivextro.

Overall conclusions on public summary of the RMP

The public summary of the RMP is acceptable.

Annexes

Specific Adverse Reaction Follow-Up Questionnaires for Safety Concerns have been removed from Annex 4 since the safety concerns for which these questionnaires were designed have been deleted from the list of safety concerns.

2.7. Overall conclusion on the RMP

The changes to the RMP proposed with submitted version 7.1 are acceptable.

The MAH is reminded that after a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so consideration should be given to the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.8. Update of the Product information

As a consequence of this variation, sections 4.1, 4.2, 4.4, 4.8 5.2, 5.3 and 6.6 of the SmPC are being updated to include information regarding use in children. The Package Leaflet (PL) is updated accordingly.

The therapeutic indication was updated to include the additional population (children < 12 years of age):

In addition, the list of local representatives in the PL has been revised to amend contact details for a number of the MAH local representatives.

Please refer to Attachment 1 which includes the approved changes to the Product Information.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Only a few changes to the text were introduced and these are specifically related to the scope. The proposed changes to the PLs of the film-coated tablets and of the powder for concentrate for solution for infusion are not significant in terms of the readability and as such will not have any impact in the approved PLs whose information remains understandable by the patients.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

ABSSSI represents a subset of SSTI (also known as SSSI) comprising cellulitis, erysipelas, major cutaneous abscess, and wound infection. *Staphylococcus aureus* is the primary pathogen responsible for ABSSSI in paediatric and adult patients and accounts for at least 60% of ABSSSI cases globally, with substantial contributions from both MRSA and MSSA. Another important pathogen in ABSSSI in both paediatric and adult patients is the Group A beta-haemolytic streptococcus, *Streptococcus pyogenes* (i.e., GAS). Other beta-haemolytic streptococcal species and anaerobic gram-positive organisms can also be responsible for ABSSSI, with considerable dependence on anatomical location of the site of infection.

3.1.2. Available therapies and unmet medical need

Recommended standards of care for ABSSSI in paediatric patients include empiric treatment with an antibacterial agent with broad-spectrum activity against gram-positive pathogens, including *S. aureus* (e.g., penicillins or macrolides). Empiric treatment of ABSSSI in paediatric patients can include coverage for MRSA; therapeutic options include vancomycin, TMP/SMX, doxycycline/minocycline, ceftaroline, and daptomycin. Clindamycin is an option for ABSSSI due to gram-positive bacterial infections, but it is not universally effective against MRSA.

The approved treatment options for paediatric patients <12 years of age with ABSSSI due to MRSA are limited by adverse effects, DDIs, susceptibility patterns, gaps in coverage of common causative pathogens in ABSSSI, ease of use, route, frequency, and duration of treatment. Current treatment options for ABSSSI due to MRSA have been associated with adverse effects including nephrotoxicity, ototoxicity, infusion reactions, hepatotoxicity, photosensitization, haematological toxicities/myelosuppression, lactic acidosis, peripheral neuropathy, and optic nerve disorders.

Many approved therapies for paediatric patients have limitations due to antibiotic resistance, leading to gaps in coverage of common causative pathogens in ABSSSI and some have age restrictions. For example, tetracycline antibacterial agents should not be administered to patients <8 years of age due to effects on tooth development. Daptomycin should not be administered to patients <1 year of age.

3.1.3. Main clinical studies

The MAH submitted new clinical data derived from three (two Phase 1 and one Phase 3) clinical studies to support the use of SIVEXTRO for the treatment of ABSSSI in a new target population: patients < 12 years of age.

The two Phase 1 studies, MK-1986-013 (P013) and MK-1986-014 (P014), evaluated the PK, safety, and tolerability of a single oral or IV dose of tedizolid phosphate in participants 2 to <12 years of age (P013) and from birth to <2 years of age (P014). P014 also included multiple-dose neonatal (full-term and preterm neonates from birth to <28 days of age) cohorts to evaluate the PK, safety, and tolerability of multiple IV doses of tedizolid phosphate in the neonatal age group.

The Phase 3 study, MK-1986-018 (P018), evaluated the safety and efficacy of multiple IV and oral doses of tedizolid phosphate in participants <12 years of age.

3.2. Favourable effects

The observed tedizolid PK data in children < 12 years of age in Studies P013, P014 and P018 provided data to update the previously developed adolescent popPK model. The population PK analyses demonstrated that the proposed dosing regimens for tedizolid resulted in predicted AUC and C_{max} generally similar across the different weight bands and to those in adults.

In Study 018, the clinical success rates at the TOC visit (22 to 29 days after first dose) were high (>90%) and comparable in the tedizolid and comparator groups in both the ITT (all randomized participants) and CE-TOC populations.

The microbiological response rate (eradication or presumed eradication) at the TOC visit was high and comparable for both groups, in both MITT (97.8% and 100%, respectively) and ME (100% for both groups) populations.

3.3. Uncertainties and limitations about favourable effects

In Study 014, multiple dose data in neonates was poorly collected with 4 out of 7 subjects not being included in the study.

The MAH confirmed that the observed concentrations on the 4 excluded neonates (1 preterm and 3 full term) were not biologically plausible and significantly deteriorated the performance of the PopPK model. Examination of the demographics and the study records, including dose preparation and administration, did not offer a clear explanation for the observations in the 4 neonates, and thus, it is only based on the plasma levels that the exclusions are supported. In fact, these concentrations are, indeed, implausible, as they are several orders of magnitude lower compared to all remaining participant data, including other neonatal data. Although a logical explanation for these outlier data is not possible to be found, its exclusion was supported.

Taking in consideration that tedizolid shows linear and time-invariant kinetics, that there was a good characterization of the PK in single dose, the expected accumulation is not high and the available multiple-dose profiles do not show a significant departure from the expected behaviour, it was agreed that the population PK model is appropriately characterizing the PK in the neonatal population.

3.4. Unfavourable effects

No new safety signals were identified from the submitted paediatric studies that suggest a different safety profile from the adult population.

3.5. Uncertainties and limitations about unfavourable effects

The limited safety database limits the detection of adverse events. This is of particular significance for patients <28 days, given the known safety profile of tedizolid and due to the limitations found in the pK analysis for this population. Nevetheless, no new safety signals were identified from the submitted paediatric studies suggesting a potential different safety profile from the adult population.

3.6. Effects Table

Effects Table for Sivextro for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult patients and paediatric patients

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PK similarity	AUC and C_{max} comparison based on PopPK modelling		<12 years of age	>12 years of age	predicted AUC and C_{max} generally similar across the different weight bands and to those in adults; Limited data for patients <28 days of age	
Clinical response	clinical success rates at the TOC visit (ITT population)	N (%)	Tedizolid 70(93.3%)	Comparator 23(92.0%)	Results from a single study[a]	
Microbiological response	microbiological response at the TOC visit (ME population)	%	Tedizolid 100%	Comparator 100%	Results from a single study[a]	
Unfavourable Effects						
Myelosuppression	Proportion of paediatric participants in the safety population with AEs of anaemia, thrombocytopenia, or neutropenia	%	Tedizolid Anaemia: 0 thrombocytopenia: 1.3 neutropenia: 1.3	Comparator Anaemia: 0 thrombocytopenia: 0 neutropenia: 0	Results from a single study[a]	
Myelosuppression	Proportion of pediatric participants in the safety population with PCS abnormal values for Hgb, Plt, or ANC[b]	%	Tedizolid Hgb 0.6 Plt 3.9 ANC 2.6	Comparator Hgb 2.0 Plt 2.0 ANC 2.0	Results from pooled studies in participants 28 days to <18 years of age[c]	

AE=adverse event; ANC=absolute neutrophil count; Hgb=hemoglobin; ITT=intent-to-treat; LLN=lower limit of normal; ME=microbiologically evaluable; PCS=potentially clinically significant; Plt=platelets; TOC=test of cure.

Notes:

[a] Results from P018, the Phase 3 randomized active-controlled study of tedizolid versus comparator in participants <12 years of age with ABSSSI.

[b] PCS hematologic low values are defined as values that are <75% of LLN (or <50% of LLN for ANC).

[c] Hemoglobin, platelets, and neutrophils were evaluated across participants receiving multiple doses of tedizolid phosphate (in P012, P014, and P018) for postbaseline changes consistent with PCS hematologic low values.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The observed tedizolid PK data in children < 12 years of age in Studies P013, P014 and P018 provided data to update the previously developed adolescent popPK model. The population PK analyses demonstrated that the proposed dosing regimens for tedizolid resulted in predicted AUC and C_{max} generally similar across the different weight bands and to those in adults.

In Study 018, the clinical success rates at the TOC visit (22 to 29 days after first dose) were high (>90%) and comparable in the tedizolid and comparator groups in both the ITT (all randomized participants) and CE-TOC populations.

The microbiological response rate (eradication or presumed eradication) at the TOC visit was high and comparable for both groups, in both MITT (97.8% and 100%, respectively) and ME (100% for both groups) populations.

The high clinical success rates in the tedizolid and comparator groups provide reassurance of an adequate efficacy of tedizolid in the age groups included in the sought extension of indication.

No new safety signals were identified from the submitted paediatric studies that suggest a different safety profile from the adult population.

3.7.2. Balance of benefits and risks

PK analyses show comparable drug exposure in the paediatric population and adults, which is further supported by the submitted efficacy data.

Therefore, if used according to the proposed SmPC, tedizolid is considered to be appropriate for use in children aged < 12 years of age.

3.7.3. Additional considerations on the benefit-risk balance

For Sivextro 200 mg powder for concentrate for solution for infusion, within this variation, the MAH included the assessment of the dosing accuracy of infusion pumps, as well as the evaluation of the in-

use compatibility of the Tedizolid Phosphate Powder for Concentrate for Solution for Infusion with dextrose 5% in water (D5W).

Module 3.2.P.2.6 of the Dossier (Compatibility), as well as section 6.6 of the SmPC, and the Package Leaflet were updated accordingly.

The MAH justified the change based on the need of the following studies for the development of a paediatric formulation of powder for concentrate for solution for infusion:

1. Assessment of dosing accuracy with the proposed method of administration and dosing devices for children under 3 months of age:

    a. Dosing for children via elastomeric infusion pump (HomePump Eclipse) for less than 40 mL of dose.

    b. Dosing for children via a syringe infusion pump (Medfusion 3500) for less than 40 mL of dose

2. Evaluation of the in-use compatibility of Tedizolid Phosphate Powder for Concentrate for Solution for Infusion when diluted with dextrose 5% in water (D5W) and stored at 2–8°C and ambient conditions for up to 40 h.

The remaining compatibility tests performed for the adult formulation, as described in 3.2.P.2.6 Compatibility – Injection, also apply to the paediatric formulation.

The experimental design was applied to the drug product dissolved in D5W. Dosing accuracy, assay and related substances, pH, appearance, and clarity of solution were studied.

Dosing Accuracy - Studied for HomePump Eclipse Infusion Pump and the results showed that the dosing volumes of 25 mL, 30 mL, and 40 mL were precise and accurate. A lower volume of 10 mL, though precise, showed a high bias of +15% and was thus not recommended, which was consistent with the user manual. In addition, Syringe infusion pump Medfusion 3500 was used for a dose volume of 2 mL up to 40 mL and the test results were accurate and precise in the range.

Assay and Related Substances - Results show no significant changes in assay values for both 2-8°C and ambient laboratory conditions for up to 40 h. The degradation products also showed no significant change.

pH determination – Solution showed an initial pH range of 7.2-7.3 immediately after preparation. After storage at 2-8 °C for up to 40 h, the pH values were essentially stable at 7.2. After storage at ambient laboratory conditions for up to 40 h, the pH values were also stable at 7.2.

Appearance and clarity – These parameters remained unchanged throughout the studies under the tested conditions. Physical observation indicated the solution was clear, colourless, and free from visible particles for all samples for up to 40 h, when stored at either 2-8°C or at ambient conditions.

However only visible particles were investigated, whereas acceptance criteria should also include sub-visible particles, according to the ICH Q6A, section 3.3.2.3.e) *Parenteral products - Particulate matter* (refer also to ICH 4B, Annex 3).

In section 6.6 of the SmPC, the MAH provided a table giving the instructions for reconstitution and dilution of the vials for the paediatric population by body weight. This had been agreed with the PDCO and was part of the compliance check prior to the submission of this paediatric extension procedure (compliance report EMEA-C3-001379-PIP01-12-M08).

3.8. Conclusions

The overall B/R of Sivextro in the sought indication is positive. The procedure is recommended for approval.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of paediatric patients aged from birth to less than 12 years for SIVEXTRO, based on final results from studies MK-1986-013, MK-1986-014 and MK-1986-018. MK-1986-013 is a single-dose trial to evaluate pharmacokinetics (PK) and safety of oral and intravenous (IV) administration of tedizolid phosphate in patients from 2 years to <12 years of age; MK-1986-014 is an open-label, multicentre, 2-part, single and multiple dose study to assess the PK of tedizolid phosphate and its active metabolite, tedizolid, and the safety of tedizolid phosphate following single and multiple dose IV and single oral dose. MK-1986-018 is a randomised, active controlled, investigator-blind, multicentre trial to evaluate safety and efficacy in patients from birth to less than 12 years of age. In addition, changes to the posology for patients ⩾12 years of age are proposed. A weight-banded IV dosing regimen is proposed for all paediatric patients <35 kg of body weight, including those ⩾12 years of age. To maintain alignment between the IV and oral dosing regimens, the 200 mg tablet dosing regimen is proposed for paediatric patients weighing ⩾35 kg only, regardless of age. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement minor editorial corrections. Version 8.0 of the RMP is being approved with this procedure.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0340/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Sivextro-H-C-002846-II-0054