28 May 2020
EMA/316574/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: **Sivextro**

International non-proprietary name: tedizolid phosphate

Procedure No. EMEA/H/C/002846/II/0035

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.

Table of contents

List of abbreviations

Abbreviation	Definition
ABSSSI	Acute bacterial skin and skin structure infections
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
CA-MRSA	Community-associated methicillin-resistant *Staphylococcus aureus*
CDAD	*Clostridium difficile*-associated diarrhea
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CE-EOT	Clinically evaluable at end of therapy
CE-TOC	Clinically evaluable at test of cure
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum concentration
CoNS	Coagulase-negative staphylococci
CPK	Creatine phosphokinase
CSR	Clinical Study Report
cSSSI	Complicated skin and skin structure infections
cSSTI	Complicated skin and soft tissue infections
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DAIDS	Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health
EMA, EMEA	European Medicines Agency
EOT	End of therapy
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FA	Free acid
FDA	Food and Drug Administration
GAS	Group A streptococcus
ITT	Intent-to-treat
IV	Intravenous(ly)
LFU	Late follow-up
LLN	Lower limit of normal
MAO	Monoamine oxidase
ME	Microbiologically evaluable

Abbreviation	Definition
MIC	Minimum inhibitory concentration
MITT	Microbiological intent-to-treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
PCS	Potentially clinically significant
PD	Pharmacodynamic(s)
PDCO	Paediatric Development Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PSP	Pediatric Study Plan
PTA	Probability of target attainment
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
sNDA	Supplemental New Drug Application
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
SSSI	Skin and skin structure infections
SSTI	Skin and soft tissue infections
T_{max}	Time of maximum concentration
TMP/SMX	Trimethoprim/sulfamethoxazole
TOC	Test of cure
UK	United Kingdom
ULN	Upper limit of normal
US	United States
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 28 August 2019 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, II and IIIB

Extension of Indication (treatment of ABSSSI in adults) to include adolescent population from 12 years old and older for Sivextro; as a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. Sections 1 and 2 of the Package Leaflet are updated in accordance.
The updated RMP version {5.1} has also been submitted.

In addition, the (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.1.

The variation requested amendments to the Summary of Product Characteristics, Annex II 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 an EMA Decision (P/0031/2018) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0031/2018 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 Rapporteurs appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	28 August 2019
Start of procedure:	30 November 2019
CHMP Rapporteur Assessment Report	27 January 2020
PRAC Rapporteur Assessment Report	4 February 2020
PRAC members comments	5 February 2020
PRAC Outcome	13 February 2020
CHMP members comments	17 February 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	25 February 2020
Request for supplementary information (RSI)	27 February 2020
CHMP Rapporteur Assessment Report	14 May 2020
CHMP members comments	18 May 2020
Updated CHMP Rapporteur Assessment Report	20 May 2020
Opinion	28 May 2020

2. Scientific discussion

2.1. Introduction

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 (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 initiation complex. Tedizolid phosphate is currently approved in >50 countries including the EU and US for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in patients 18 years of age or older at a dosage of 200 mg administered once daily, either orally or as an intravenous (IV) infusion over 1 hour, for 6 days.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

The data provided by the MAH support the application for expanding the current use of tedizolid phosphate in adult patients with ABSSSI to include use in adolescent patients 12 to <18 years of age with ABSSSI. The proposed dosage for adolescents is the same as that for adults. This is based on similarities in the exposures between adolescent and adult patients given the same 200 mg daily dose. The

pharmacokinetic (PK) properties of tedizolid were similar in adults and adolescents and there were no meaningful changes in exposure in adolescents when compared to adults. In addition, the clinical data in this application demonstrate that tedizolid phosphate, when administered IV and/or orally once daily for 6 days, is efficacious and well tolerated in adolescent patients with ABSSSI.

After the completion of the initial marketing authorization application, juvenile toxicity studies in neonatal rats were conducted according to the approved Paediatric Investigation Plan. The purpose of the juvenile toxicity studies was to support the clinical investigations in paediatric groups <12 years of age. Clinical studies are ongoing to evaluate the efficacy, safety, and PK of tedizolid phosphate in patients <12 years of age. The juvenile toxicity studies submitted were included in the EU 5-year renewal (R/31), and assessed by CHMP in that context.

2.2.2. Pharmacology

No new non-clinical pharmacodynamic studies have been conducted to support the extension of indication in adolescent patient population, which was considered acceptable by the CHMP.

2.2.3. Pharmacokinetics

No new non-clinical pharmacokinetic studies have been conducted to support the extension of indication in adolescent patient population, which was considered acceptable by the CHMP.

2.2.4. Toxicology

A comprehensive toxicology programme to support the initial marketing authorisation (IMAA) of tedizolid phosphate included: oral (PO) and IV repeat-dose toxicology in rats (up to 3 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, juvenile toxicity, and impurity qualifications. Carcinogenicity studies were not conducted given the short clinical exposure duration.

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

As discussed in the initial marketing authorization application, exposure margins in the oral repeat dose toxicity studies based on area under the curve (AUC) values at the no observed adverse effect levels (NOAELs) ranged from 3.7- to 7.4-fold for rats and 3.0- to 6.8-fold for dogs. Exposure margins for IV administration ranged from 3.3- to 4.3-fold in rats and 3.1- to 3.2-fold in dogs.

In a rat fertility study, the exposure margin at the NOAEL was approximately 4 to 5-fold greater than the plasma AUC value in adult humans at the 200 mg dose. In mouse and rat studies developmental toxicity studies, there were no teratogenic effects or embryo-lethality at exposures approximately 4- and 6-fold higher than the adult human exposure. In pregnant rats administered tedizolid phosphate during organogenesis through lactation, there was no evidence of foetal toxicity, developmental delays, or impaired reproduction in the offspring at exposure approximately equivalent to the human exposure.

In the juvenile rat toxicity studies, tedizolid phosphate was administered by oral gavage to rats for 50 consecutive days beginning when the rats were neonatal (post-natal day 7). The developmental stages of this treatment period in rats encompass the ongoing Paediatric study with patients <12 years of age. Overall, no unique target organs of toxicity were identified in the juvenile rat studies compared to those

identified in the repeat oral dose toxicity studies in older rats. The target organs of toxicity included the hematopoietic and gastrointestinal system. Poor tolerability (including weight loss and mortality) was observed in the juvenile rat studies with tedizolid phosphate at a lower exposure level compared to the exposure level associated with similar changes in adult rats.

No new non-clinical toxicology studies have been conducted to support the adolescent patient population. Below, the following points are addressed: 1) the developmental age of rats used in repeat dose toxicity studies compared to the human adolescent age range, and 2) a comparison of the PK values in adults to PK values in adolescents at the therapeutic dose of 200 mg once/day.

- Relevance of non-clinical toxicity studies (coverage of Adolescent Age Range)

Rats that are 45-90 days of age generally correspond to the human adolescent age of 12-16 years. Several GLP repeat dose toxicity studies in rats were conducted with tedizolid phosphate using peripubertal rats. The age of the rats used in these studies is shown in the below table.

List of Studies and Approximate Age at Study Start

Study Type/duration	**Study Number**	**Approximate Age at Study Start**
Rat IV toxicity/28-day	TOX-08-0701-009	49 days
Rat oral toxicity/28-day	TOX-07-0701-014	42 days
Rat oral toxicity/3-months	TOX-11-0701-027	49-56 days
Rat oral fertility and early embryonic development	TOX-08-0701-026	Males: 56 days; Females: 77 days

IV = Intravenous

Note: Studies have been previously submitted to the initial marketing authorization application

The age of the rats and the duration of dosing in these studies provides appropriate coverage of the human adolescent development age range, and no additional non-clinical studies were required to support the use of tedizolid phosphate in this age group.

- Comparison of PK values in adults and adolescents

In the initial marketing authorization application, the exposure margins were based on the animal plasma exposure values at the NOAEL compared to the adult human plasma exposure at the 200 mg dose. At the human dose of 200 mg tedizolid phosphate once daily, the geometric mean tedizolid steady-state plasma AUC0-24 values in adults were 28.6 µg•h/mL (IV) and 24.6 µg•h/mL (PO); and the Cmax plasma concentrations were 3.0 µg/mL (IV) and 2.2 µg/mL (PO).

In comparison, in adolescents at 200 mg the geometric mean tedizolid steady-state plasma AUC0-24 values were 29.4 µg•h/mL (IV) and 27.9 µg•h/mL (PO); and the Cmax plasma concentrations were 3.68 µg/mL (IV) and 2.63 µg/mL (PO). The population PK model-predicted tedizolid exposure is slightly higher in adolescent patients compared to adult patients due to the effect of body weight at the approved adult dosage. Regardless of the slight difference, the adolescent exposure distributions were within the adult exposure distributions.

Overall, the slight differences in Cmax and AUC0-24 values in adults compared to adolescents has no meaningful impact on the calculated safety margins. The safety margins in the initial marketing authorization application are therefore applicable to the adolescent population.

The CHMP considered that the comprehensive non-clinical programme conducted with tedizolid phosphate included in the submission of the initial marketing authorization application for adult patients is applicable and provides non-clinical safety support for the addition of the adolescent patients 12 to <18 years of age. The age of the rats in the repeat dose toxicity studies provides appropriate developmental age coverage of the human adolescent group. In addition, the dosing regimen for adults and adolescents is the same, and the resulting pharmacokinetic and clinical safety profile is similar in both populations.

2.2.5. Ecotoxicity/environmental risk assessment

The MAH submitted an environmental risk assessment. The studies annexed had already been evaluated when this medicinal product was initially authorised and afterwards, through the assessment of a variation type IB in 2015: EMEA/H/C/002846/IB/0005.

The maximum PECsw previously calculated (1.0 µg/L) was used for the risk analysis, because it comprises the default value for the percentage of market penetration (the worst-case scenario). An update on the environmental risks of the product was performed focussing the EC10 of Blue-Green Algae, Daphnia and Fish and the endpoint for the sediment toxicity test as well as the PEC sediment, which were normalised to 10% organic carbon.

The PEC/PNEC ratios remain below 1.0 and 0.1 for surface water / groundwater / sediment and microorganism respectively.

For this variation, the MAH, considering the maximum PECsw of 1.0 µg/L and the studies previously submitted and assessed, corrected the environmental risks on the following issues:

a) PNECs based on EC10 values;

Study	Endpoint	Toxicity (mg/L)	Method
Activated Sludge Respiration Inhibition	NOEC	100	OECD 209 [8]
Blue-Green Algae (Cyanobacteria)	E_rC_{10}	0.098	OECD 201 {04VBMM }
Daphnid Reproduction	EC_{10}	1.1	OECD 211 [10]
Fish Early Life Stage	EC_{10}	0.021	OECD 210 [11]

b) Endpoint for the sediment toxicity test normalised to 10% organic carbon.

$$NOEC_{standard\ sediment} = 100\ mg/kg\ x\ \frac{10\%}{1.9\%} = 526.36\ mg/kg$$

c) PECsediment normalised to 10% organic carbon. The calculations were based on the Koc and the Kpsusp was calculated with the factor 0.1 to normalise to 10% OC.

An extract from the ERA summary table with the updated data is shown below:

Compartment	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC
Surface water	1.0	2.1	4.7E-01
Groundwater	0.25	110	2.3E-03
Wastewater treatment facility (Microorganism)	1.0	10,000	1.0E-04

Compartment	PEC (mg/kg)	PNEC (mg/kg)	PEC/PNEC
Sediment	0.043	5.3	8.3E-03

Tedizolid does not exhibit potential for bioaccumulation based on logPow, but is stable in sediment. No risk to the surface water, ground water, microorganisms and sediments are anticipated.

2.2.6. Discussion on non-clinical aspects

Because the non-clinical studies submitted with the initial marketing authorization application for adult population provided adequate support for the proposed adolescent population, no additional non-clinical studies were submitted with this application. The data provided at the time of initial marketing authorization are applicable and provide adequate non-clinical safety support for the addition of adolescent patients 12 to <18 years of age.

In terms of toxicology studies that support the extension of indication to the adolescent population, the MAH discussed the juvenile rat toxicity studies submitted at the time of the initial marketing authorization application. The age of the rats in the repeat dose toxicity studies was appropriate. In addition, the dosing regimen for adults and adolescents is the same, and the resulting pharmacokinetic and clinical safety profile is similar in both populations.

The MAH submitted an updated Environmental Risk Assessment for this extension of indication. The PEC/PNEC ratios remain below 1.0 and 0.1 for surface water/ groundwater/ sediment and microorganism respectively. No risk to the surface water, ground water, microorganisms and sediments are anticipated.

Tedizolid does not exhibit potential for bioaccumulation based on logPow, but is stable in sediment.

2.2.7. Conclusion on the non-clinical aspects

The CHMP considered that the comprehensive non-clinical programme conducted with tedizolid phosphate included in the submission of the initial marketing authorization application for adult patients is applicable and provides adequate non-clinical safety support for the addition of the adolescent patients 12 to <18 years of age. The age of the rats in the repeat dose toxicity studies provides appropriate developmental age coverage of the human adolescent group.

The dosing regimen for adults and adolescents is the same, and the resulting pharmacokinetic and clinical safety profiles are similar for the two populations.

The extended indication does not lead to a significant increase in environmental exposure further to the use of tedizolid, which is therefore not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

A comprehensive clinical pharmacology programme was conducted to support the initial marketing authorization application for the use of tedizolid phosphate at a dose of 200 mg once daily for adult population. No new clinical pharmacology or preclinical PD studies were conducted to specifically support the adolescent ABSSSI program.

The clinical pharmacology profile of tedizolid was established in several Phase 1 studies that evaluated the safety, tolerability, and PK of tedizolid following administration of tedizolid phosphate. Studies also evaluated the effect of intrinsic and extrinsic factors on tedizolid PK as well as the potential for DDIs, and the potential effect of the clinical therapeutic dose and a supratherapeutic dose of tedizolid phosphate on the QTc interval. These studies were previously submitted, reviewed, and approved as part of the initial marketing authorization application and were conducted primarily in adults. However, the profile also included a Phase 1 study in adolescents, Study MK-1986-026 (P026, also known as TR701-111).

P026 was a single dose PK study in adolescent participants 12 to <18 years of age who were receiving prophylaxis for or had a confirmed or suspected gram-positive bacterial infection and were receiving concurrent antibiotic treatment with gram-positive antibacterial activity.

Tedizolid phosphate is approved as a 200 mg tablet formulation and as a vial for IV infusion. No new formulation was developed for the adolescent ABSSSI programme, and the same dosage and formulations approved for adults are proposed for adolescents.

An additional study, and the main study in support of this Extension of Indications in the adolescent population is Study MK-1986-012 (P012, also known as TR701-122), completed since the initial marketing authorization application, which assessed tedizolid's PK in adolescent patients with ABSSSI.

P012 was a randomized, assessor-blind, multicenter, comparator-controlled, global Phase 3 study of tedizolid phosphate 200 mg IV and/or orally once daily for 6 days versus comparator IV and/or orally (per local standard of care) for 10 days in adolescent patients with ABSSSI. Population PK analysis was conducted to assess tedizolid exposures in adolescent patients with ABSSSI in P012 and compared to that of adult patients. Exposure-response analysis and Probability of target attainment (PTA) assessments were performed to assess the expected effectiveness of tedizolid at this dosage against the causative organisms of ABSSSI as well as its safety in adolescents.

GCP

The MAH 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.

- Tabular overview of clinical studies

Table 1 - Summary of the Adolescent Phase 3 Clinical Efficacy Study with Tedizolid Phosphate (P012)

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Number of Participants by Intervention Group	Study Population (N)	Key Efficacy Endpoints[c]/Results
P012[a] (Completed) [Ref. 5.3.5.1: P012MK1986] 19 sites (9 countries and 3 regions [North America, Europe, South Africa])	Randomized, tedizolid: comparator (3:1), assessor-blind, multicenter, active-comparator, parallel-group (Participants 12 to <18 years of age with ABSSSI) Duration: 158 weeks	Tedizolid phosphate 200 mg IV and/or orally once daily for 6 days (91 randomized/ 91 treated/ 88 completed) Active comparator IV and/or orally (per local standard of care) for 10 days (29 randomized/ 29 treated/28 completed)	Gender: 75M/45F Median age: 15 years (Age range: 12 to 17 years)	• Percentage of participants with clinical success (per blinded investigator's assessment) at the TOC Visit in the ITT and CE-TOC Analysis Sets The rate of clinical success at the TOC Visit (18 to 25 days after the first infusion) was high (>93%) and comparable between treatment groups in the ITT and CE-TOC Analysis Sets. • Percentage of participants with early clinical success (⩾20% reduction in lesion size, as measured by blinded investigator) at the 48 to 72 Hour Visit in the ITT Analysis Set The rate of early clinical success (at the 48 to 72 Hour Visit) was high (>92%) and comparable between treatment groups in the ITT Analysis Set. • Percentage of participants with clinical success (per blinded investigator's assessment) at the EOT Visit (Day 11) in the ITT and CE-EOT Analysis Sets The rate of clinical success at the EOT Visit (Day 11 + 2 days) was high (>96%) and comparable between treatment groups in the ITT and CE-EOT Analysis Sets.

ABSSSI=acute bacterial skin and skin structure infections; CE-EOT=clinically evaluable at end of therapy; CE-TOC=clinically evaluable at test of cure CTD=Common Technical Document; EOT=end of therapy; F=female; ITT=intent-to-treat; IV=intravenous(ly); M=male; TOC=test of cure.
a MK-1986-012, also known as TR-701-122.
b Enrolled participants.

2.3.2. Pharmacokinetics

Tedizolid phosphate (a prodrug) is rapidly converted to tedizolid (the active moiety) after IV and oral administration and measurable PK data are limited for tedizolid phosphate. The PK properties of tedizolid are similar in adults and adolescents.

Previous evaluation of tedizolid PK supporting the currently authorized dosage of 200 mg of tedizolid phosphate administered once daily orally or as an IV infusion over 1 hour for 6 days for the treatment of ABSSSI in adult patients was presented in the initial marketing authorization application.

Absorption, Distribution, Elimination

Tedizolid is rapidly absorbed after oral administration of tedizolid phosphate in adults, with Cmax achieved within 3 hours. Tedizolid exhibits high absolute bioavailability (>90%) after oral administration of tedizolid phosphate; no dosage adjustment is required in switching between IV and oral administration. Although Tmax is delayed by approximately 6 hours and Cmax decreases approximately 26% when tedizolid phosphate is administered with a meal compared to fasting, food has no clinically meaningful effect on AUC after oral administration. AUC/MIC is the PK/PD index associated with antibacterial efficacy; therefore, tedizolid phosphate can be administered without regard to food.

After IV administration of tedizolid phosphate to adolescent participants in P026, Cmax was achieved at the end of infusion. The half-life was approximately 7 hours after a single dose. After oral administration

of tedizolid phosphate, tedizolid demonstrated rapid absorption with Cmax achieved within 4 hours, and bioavailability was approximately 89% after a single dose. The clearance of tedizolid was estimated to be 6.3 L/h and the volume of distribution was 54.2 L in adolescent participants, which were similar to those in healthy adult participants.

The binding of tedizolid to human plasma proteins is approximately 70% to 90%. The mean steady state volume of distribution of tedizolid in healthy adult participants following a single IV dose of tedizolid phosphate 200 mg ranged from 67 to 80 L (approximately twice total body water volume). Tedizolid had high passive permeability and was distributed extensively and rapidly into interstitial tissue space. Distribution is not expected to be affected by increases in vascular permeability associated with inflammation in infected patients.

Tedizolid is eliminated mostly as a sulfate conjugate in feces with renal excretion as a minor pathway. In adults, the average terminal half-life of tedizolid is approximately 12 hours.

Study P012

Tedizolid pharmacokinetics were assessed as part of P012. Population PK modeling and simulation and Probability of target attainment (PTA) analyses were performed as part of P012 to bridge efficacy from adult to adolescent patients with ABSSSI. A total of 5 blood samples for the quantification of tedizolid were collected from each participant in the tedizolid group over 3 days (Day 1, 2, or 3 and Day 7) after initiation of dosing. The PK data were included in the updated population PK analysis with other available PK data and used to simulate the individual exposure levels in adolescent participants.

A population PK modeling approach was used to evaluate tedizolid PK in adolescent patients with ABSSSI by updating the previously developed population PK model. This model described the PK of tedizolid using a two-compartment model with linear elimination and sigmoidal absorption.

The updated model integrated all available PK data in the clinical programme including PK data from adult healthy participants and patients with active bacterial infection (10 Phase 1 studies, 2 Phase 2 studies, and 4 Phase 3 studies including data from Japanese and Chinese studies in adult participants with ABSSSI) and adolescent patients (1 Phase 1 study in adolescent participants with confirmed or suspected gram-positive bacterial infection (P026) and 1 Phase 3 study in adolescent participants with ABSSSI (P012)).

Intensive PK sampling was available from the Phase 1 studies, whereas sparse PK sampling was available from the Phase 2 and Phase 3 studies. In total, 1,312 patients, including 223 healthy adult participants and 111 adolescent patients, were studied, with participants receiving doses in the range of 40 to 600 mg of tedizolid phosphate. The population PK analysis was performed using a non-linear mixed-effects modeling approach.

The structure of the final model was a 2-compartment disposition model with linear elimination. Covariate analyses were conducted, and weight was identified as the significant covariate impacting the clearance and volume parameters. Age was not found to be a significant covariate.

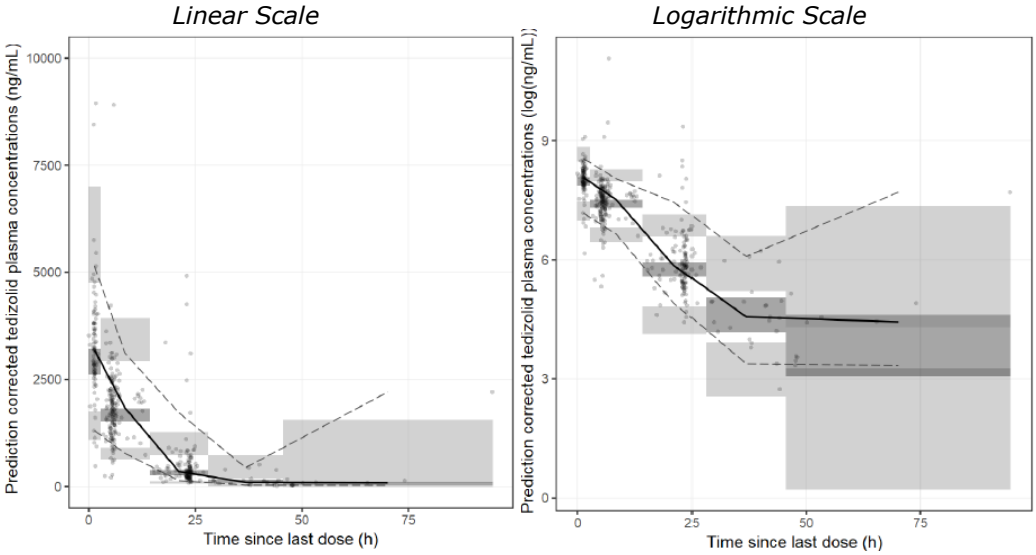
Population PK modelling

Population PK modeling was conducted with available plasma PK data from Phase 1 through Phase 3 studies in adult and paediatric participants, including data from P012. In combination with PTA analyses, the population PK results showed that the tedizolid phosphate dosage proposed for the adolescent ABSSSI indication (200 mg once daily, the same as the dosage for the adult ABSSSI indication) provided exposure comparable to that in adults who received the same dosage. This enabled bridging of efficacy

and of the clinical pharmacology properties of tedizolid from adults to the adolescent population and justifies the use of the 200 mg dose of tedizolid phosphate in adolescents with ABSSSI.

Prediction-corrected VPCs stratified by study were performed for the final model; 500 replicate simulations were conducted for each pcVPC. The pcVPCs demonstrate good agreement between the simulated and observed prediction-corrected PK profiles. Data from most of the studies could adequately be described by the model. The pcVPC in the adolescent population study (Study P012) is presented in Figure 1.

Figure 1 - Prediction-corrected VPC of the Final Model (run412s) – Study P012 Only



Abbreviations: TSLD = time since last dose, VPC = visual predictive check.
Note: Prediction-corrected VPC of the tedizolid plasma concentrations versus TSLD is presented. Within each panel, the median (bold line) and 5th and 95th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals (shaded areas) for the median (dark area) and 5th and 95th percentiles of the simulated (n = 500) data (light areas). Individual prediction corrected observations are represented by the black dots.
Note: In the linear scale plot (left panel), 3 prediction-corrected observations (>10000 ng/mL) are not shown.

Table 2 - Final Population PK Model Parameter Estimates and Bootstrap Analysis

Parameter	Final Model[A] (run412s)			FOCE Bootstrap[E] (run412s_bootstrap)	
	Fixed Effect[B] (%RSE)	IIV %CV[B] (%RSE)	Shrinkage[C,D] (%)	Fixed Effect [95% CI]	IIV %CV [95% CI]
Infusion time (h)	0.810 FIXED	8.26 FIXED	32.3	0.810 FIXED	8.26 FIXED
F1	0.857 (0.965)	–	–	0.85 [0.834, 0.867]	–
Zero-order duration (h)	0.175 (28.3)	258 (7.39)	41.1	0.475 [0.441, 0.586]	210 [179, 221]
Ka (h^{-1})	1.47 (9.25)	77.0 (8.36)	59.2	0.964 [0.923, 1.03]	74.1 [70.1, 78.4]
Lag time (h)	0.226 (0.0376)	100 (5.47)	56.8	0.178 [0.135, 0.227]	119 [101, 129]
CL (L/h)	5.39 (6.98)	32.2 (2.87)	14.6	5.48 [5.34, 5.6]	32.2 [30.4, 34.2]
~Weight [power model]	0.408 (10.2)	–	–	0.451 [0.411, 0.492]	–
~Infection (%) [linear model]	22.0 (39.3)	–	–	21.4 [18.7, 24.1]	–
Vc (L)	58.5 (3.36)	25.2 (4.67)	31.9	59.1 [57.9, 60.4]	25.3 [22.6, 28.5]
~Weight [power model]	0.903 (3.53)	–	–	0.937 [0.886, 0.975]	–
~Infection (%) [linear model]	9.87 (37.4)	–	–	10.7 [8.81, 13.9]	–
~Diabetes (%) [linear model]	-14.3 (22.2)	–	–	-14.0 [-18.6, -9.49]	–
Q (L/h)	1.43 (4.09)	–	–	1.44 [1.36, 1.52]	–
~Weight [power model]	Same as for CL	–	–	Same as for CL	–
Vp (L)	15.6 (2.41)	15.8 (8.54)	70.9	15.8 [15.3, 16.4]	16.2 [13.7, 18.5]
~Weight [power model]	0.678 (6.87)	–	–	0.677 [0.609, 0.731]	–
Correlation CL-Vc (%)	–	62.1 (5.28)	–	–	61.9 [52.1, 68.5]
Residual variability (RV)	–	–	11.7	–	–
RV for non-Phase 3 studies (%)	12.3 (1.36)	–	–	12.4 [11.8, 12.9]	–
RV for Study 104 and Phase 3 studies (fold)[F]	4.92 (4.63)	–	–	4.57 [4.13, 5.34]	–
RV for oral data (fold)[F]	2.01 (5.22)	–	–	2.23 [1.87, 2.66]	–

Abbreviations: CI = confidence interval, CL = clearance, CV = coefficient of variation, F1 = bioavailability, FOCE = first-order conditional estimation , Ka = first-order absorption rate constant, IIV = inter-individual variability, Q = intercompartmental clearance,

RSE = relative standard error; RV = residual variability, SAEM = stochastic approximation of expectation-maximization, SD = standard deviation, Vc = volume of distribution in the central compartment, Vp = volume of distribution in the peripheral compartment.
a Model parameters were estimated using SAEM from 9756 PK observations in 1312 subjects. Volumes and clearances are reported for a typical individual of 77.3 kg.
b RSE obtained from an importance sampling estimation. The relative standard errors for omega and sigma are reported on the approximate standard deviation scale (standard error/variance estimate)/2.
c η –shrinkage calculated as 1-SD(η)/ω where η are the empirical Bayes estimates drawn from a normal distribution of mean 0 and standard deviation ω.
d ε –shrinkage calculated as 1-SD(individual weighted residual).
e Mean and 95% confidence generated using only the successful runs (n = 432) from a nonparametric bootstrap (n = 1000) based on the FOCE method. Volumes and clearances are reported for a typical individual of 77.3 kg.
f Fold-increase on the square root scale.

A summary of the key predicted individual PK parameters is provided in table 3 below.

Table 3 - Summary of Study P012 Pharmacokinetic Parameters

Parameter	Geometric Mean [95% Confidence Interval]
Clearance (L/h)	5.30 [4.92, 5.71]
Central volume (L)	47.6 [44.5, 51.0]
Peripheral volume (L)	12.7 [12.2, 13.2]
Inter-compartmental clearance (L/h)	1.27 [1.24, 1.30]
Lag time (h)	0.230 [0.228, 0.231]
Zero-order duration (h)	0.206 [0.177, 0.239]
Absorption rate constant (h^{-1})	1.44 [1.42, 1.45]

The complete set of individual predicted PK profiles using the final popPK model (run412s) for Study P012 are provided. The NONMEM output for the final model and the prediction of individual tedizolid exposures are also provided.

Simulation of Exposures

Individual EBEs derived from the final popPK model (run412s) were used to predict concentrations for each adolescent subject in Study P012. Exposure parameters were then derived from the generated PK profiles and summarized by route of administration (Table 4), body weight (Table 5), and renal function (Table 6).

The $AUC_{0\text{-}24h\_last}$ and C_{min_last} were slightly lower but comparable between oral and IV administration; however, a more pronounced reduction in C_{max} was observed comparing oral with IV administration (geometric mean [95% CI] of 2.63 [2.40, 2.87] µg/mL with oral and 3.68 [3.29, 4.12] µg/mL with IV).

Table 4 - Population PK Model Predicted Exposure After Last Dose in Adolescent ABSSSI Subjects from Study P012, Stratified by <u>Route of Administration</u>

Route of Administration[A]	Geometric mean [95% Confidence Interval]		
	$AUC_{0\text{-}24h\_last}$ (µg·h/mL)	$Cmax_{\_last}$ (µg/mL)	$Cmin_{\_last}$ (µg/mL)
Oral (N = 44)	27.9 [25.2, 30.8]	2.63 [2.40, 2.87]	0.350 [0.298, 0.413]
Intravenous (N = 47)	29.4 [26.3, 32.9]	3.68 [3.29, 4.12]	0.318 [0.26, 0.389]

Abbreviations: ABSSSI = acute bacterial skin and skin structure infection, AUC0-24h_last = area under the tedizolid concentration-time curve from 0 to 24 h on the last dosing day, Cmax_last = maximum tedizolid plasma concentration on the last dosing day, Cmin_last = minimum tedizolid plasma concentration on the last dosing day, N = group size, PK = pharmacokinetic.
a The route of administration count presented is based on the administration route for the last dose received; note that 39 of the 44 subjects in the oral group have switched from IV throughout the study.

Due to the impact of body weight on disposition parameters (increasing clearance and volumes with increasing body weight), predicted exposures (AUC and C_{max} after the first and last dose) decreased with increasing body weight.

Table 5 - Population PK Model Predicted Exposure After First and Last Dose in Adolescent ABSSSI Subjects from Study P012, Stratified by <u>Weight</u>

Body weight (kg)	Geometric mean [95% Confidence Interval]			
	$AUC_{0\text{-}24h\_day1}$ (µg·h/mL)	$AUC_{0\text{-}24h\_last}$ (µg·h/mL)	$Cmax_{\_day1}$ (µg/mL)	$Cmax_{\_last}$ (µg/mL)
27.6 to 46.5 (N = 23)	32.2 [29.3, 35.4]	32.4 [29.7, 35.4]	3.32 [2.59, 4.25]	3.87 [3.43, 4.37]
46.5 to 57 (N = 23)	29.6 [25.7, 34.0]	32.2 [26.4, 39.4]	3.83 [3.45, 4.25]	3.54 [2.93, 4.29]
57 to 70 (N = 24)^	25.5 [22.7, 28.7]	27.9 [24.4, 32.0]	2.52 [1.98, 3.20]	2.97 [2.67, 3.30]
70 to 126 (N = 21)^	20.1 [18.1, 22.3]	22.6 [20.0, 25.7]	1.38 [0.965, 1.96]	2.29 [2.00, 2.63]

Abbreviations: ABSSSI = acute bacterial skin and skin structure infection, AUC0-24h_day1 = area under the tedizolid concentration-time curve from 0 to 24 h on the first dosing day, AUC0-24h_last = area under the tedizolid concentration-time curve from 0 to 24 h on the last dosing day, Cmax_day1 = maximum tedizolid plasma concentration on the first dosing day, Cmax_last = maximum tedizolid plasma concentration on the last dosing day, N = group size, PK = pharmacokinetic.
a The imbalanced group sizes are due to 4 subjects having a body weight of 70 kg.

Predicted AUC and C_{max} remained comparable across creatinine clearance (CrCL) categories (from 60 to ≥150 mL/min), and no clear trend could be identified. This is consistent with no impact of CrCL being evident from the distribution of ETA on CL and Vc *versus* CrCL. Similarly, no specific impact of age could be characterized on the PK of tedizolid.

Table 6 - Population PK Model Predicted Exposure After First and Last Dose in Adolescent ABSSSI Subjects from Study P012, Stratified by <u>Renal Function</u>

Creatinine Clearance[A] (mg/mL)	Geometric mean [95% Confidence Interval]			
	$AUC_{0\text{-}24h\_day1}$ (µg·h/mL)	$AUC_{0\text{-}24h\_last}$ (µg·h/mL)	$Cmax_{\_day1}$ (µg/mL)	$Cmax_{\_last}$ (µg/mL)
60 to 90 (N = 1)	21.2[B]	25.4[B]	2.23[B]	2.72[B]
90 to 150 (N = 56)	28.1 [26.1, 30.2]	29.4 [27.2, 31.6]	2.90 [2.46, 3.41]	3.35 [3.06, 3.67]
≥150 (N = 33)	24.0 [21.2, 27.3]	27.1 [23.1, 31.9]	2.16 [1.65, 2.84]	2.79 [2.40, 3.24]
Missing (N = 1)	43.9[B]	50.2[B]	4.61[B]	3.60[B]

Abbreviations: ABSSSI = acute bacterial skin and skin structure infection, AUC0-24h_day1 = area under the tedizolid concentration-time curve from 0 to 24 h on the first dosing day, AUC0-24h_last = area under the tedizolid concentration-time curve from 0 to 24 h on the last dosing day, Cmax_day1 = maximum tedizolid plasma concentration on the first dosing day, Cmax_last = maximum tedizolid plasma concentration on the last dosing day, N = group size, PK = pharmacokinetic.
a The creatinine clearance was calculated using the Cockcroft and Gault formula.
b EBEs 95% confidence interval could not be determined as N = 1.

The predicted exposures (AUC and C_{max} after the first and last dose) in adolescent ABSSSI subjects from Study P012 were slightly higher than those in adult ABSSSI subjects from previous Phase 2 and 3 studies (Table 7). The same was also observed for the Phase 1 adolescent PK study (Study P026). Given that weight was identified as a covariate on tedizolid clearance and volume parameters, the difference in body weight distributions in the Study P012 and the adult population studies (Studies P007, P009, and P010) may contribute to the observed exposure differences.

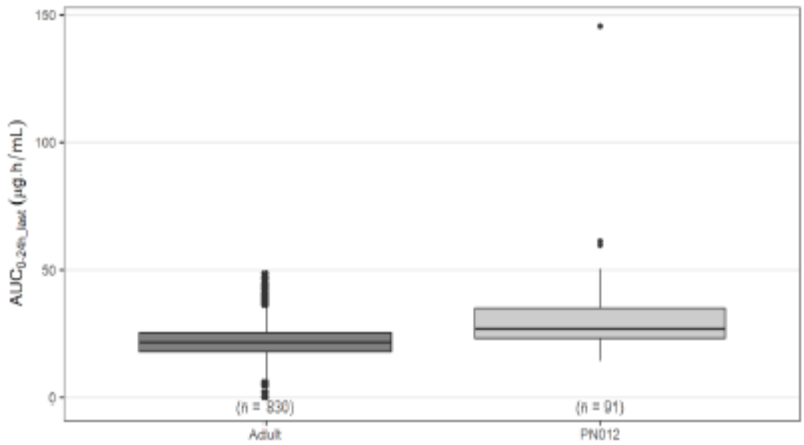
Table 7 - Population PK Model Predicted Exposure after First and Last Dose in Adolescent (Study P012) and Adult ABSSSI Subjects (Previous Phase 2 and 3 Studies)

Population	Geometric mean [95% Confidence Interval]			
	$AUC_{0\text{-}24h\_day1}$ (µg·h/mL)	$AUC_{0\text{-}24h\_last}$ (µg·h/mL)	$Cmax_{day1}$ (µg/mL)	$Cmax_{last}$ (µg/mL)
Adult (N = 830)	22.4 [21.9, 22.9]	21.0 [20.4, 21.5]	1.81 [1.73, 1.90]	2.00 [1.94, 2.06]
Adolescent, Study P012 (N = 91)	26.6 [24.9, 28.4]	28.6 [26.6, 30.8]	2.61 [2.27, 3.01]	3.13 [2.89, 3.38]

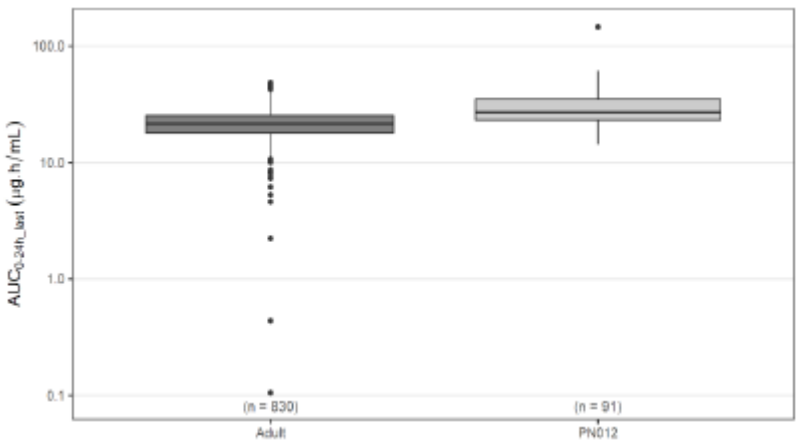
Abbreviations: ABSSSI = acute bacterial skin and skin structure infection, AUC0-24h_day1 = area under the tedizolid concentration-time curve from 0 to 24 h on the first dosing day, AUC0-24h_last = area under the tedizolid concentration-time curve from 0 to 24 h on the last dosing day, Cmax_day1 = maximum tedizolid plasma concentration on the first dosing day, Cmax_last = maximum tedizolid plasma concentration on the last dosing day, N = group size, PK = pharmacokinetic.
Note: The adult population includes ABSSSI subjects of age >18 years old from previous Phase 2 and 3 studies receiving 200 mg of tedizolid phosphate (i.e., Studies 104, 112, 113, 16099 and 16121).

Box Plots of Population PK Model Predicted AUC After Last Dose in Adolescent (Study P012) and Adult ABSSSI Subjects (Previous Phase 2 and 3 Studies)

Linear Scale



Logarithmic Scale



Abbreviations: ABSSSI = acute bacterial skin and skin structure infection, AUC0-24h_last = area under the tedizolid concentration-time curve from 0 to 24 h on the last dosing day, PK = pharmacokinetic.
Note: Box plots of the AUC0-24h_last for adults and Study P012 (adolescent) subjects are presented. The adult population includes ABSSSI subjects >18 years old receiving 200 mg of tedizolid phosphate from previous Phase 2 and 3 studies. The boxes are delimited by the 25th, 50th, and 75th percentiles; the whiskers extend to the lowest and largest values but no further than 1.5 times interquartile range from the hinge. The dots beyond the whiskers are outliers and are represented individually.

Although the exposure was slightly higher in adolescents, the distribution of exposures between adolescent and adult population was substantially overlapping.

Safety subgroup analysis per body weight

Upon CHMP request, a safety subgroup analysis per body weight in Study P012 was performed, in order to identify any safety signals due to overexposure in low-weight patients with the proposed dose regimen.

Evaluation of safety *vs*. exposure/weight focused on potentially clinically significant (PCS) abnormal hematological values [platelets, hemoglobin and absolute neutrophil count (ANC)], PCS abnormal transaminase values, and overall treatment emergent adverse events. For each of these categories, the number of subjects was small, and consequently an *exploratory* exposure-safety analysis was performed to evaluate whether there was any trend in PCS values correlating with higher exposure in low-weight subjects with the proposed dose regimen. Exposure comparisons used a re-estimated population PK model with fixed exponent values (0.75 for CL and Q; 1.0 for Vc and Vp) as also requested by CHMP. The distribution of exposures (AUC, C_{max}, and C_{min}) in adolescent subjects in P012 who experienced a PCS abnormal hematological value or any treatment emergent adverse event was found comparable to the distribution of exposures in subjects who did not experience any PCS value or treatment emergent adverse events.

Adolescent patients with ABSSSI in P012 who received the 200 mg tedizolid phosphate dose showed a small increase in tedizolid exposure with decreasing body weight. However, the effect of body weight on the pharmacokinetic profile was not considered clinically meaningful as there was no indication of an exposure-safety relationship in the exploratory exposure-safety analyses, either in the original population model (presented in Module 2.7.2 of the variation application) or based on the results from the re-estimated population PK model; overall, these analyses did not demonstrate trends suggesting a safety concern in the lowest weight quartile. These results support a lack of relationship between the PK/PD of tedizolid and safety with no identified safety concerns in low-weight adolescent patients receiving the recommended 200 mg dose of tedizolid phosphate once daily for 6 days.

The CHMP acknowledged that the requested exposure-safety analysis for the adolescent population was performed, including a safety subgroup analysis per body weight in Study P012. A small increase in tedizolid exposure with decreasing body weight was observed in adolescent patients with ABSSSI who received the 200 mg tedizolid phosphate dose. However, the effect of body weight on the pharmacokinetic profile was not considered clinically meaningful as there was no indication of an exposure-safety relationship, based on the results obtained with both the original population model and the re-estimated popPK model (with fixed exponent values).

The CHMP concluded that there are no particular safety concerns regarding the administration of the recommended dose of tedizolid phosphate (200 mg once daily for 6 days) to low-weight adolescent patients

Dose proportionality and time dependencies

In adults, tedizolid exhibits a linear PK profile with dose-proportional increases in exposure after single doses from 50 to 1200 mg of tedizolid phosphate, with minimal accumulation in exposure (approximately 30%) after multiple doses compared to a single dose and achievement of steady state within 3 days. Single-dose PK is predictive of the multiple-dose profile, indicating time-independent PK.

After a single oral or IV dose of tedizolid phosphate 200 mg, tedizolid exposure in adolescent participants in P026 was comparable to that previously observed in adults.

Special populations

Previous population PK analysis did not identify any clinically significant effect of intrinsic factors (age, body weight (obesity/BMI), gender, race/ethnicity, renal impairment (with or without dialysis), and hepatic impairment) on tedizolid PK in adults.

By integrating data across studies and populations, including adolescent participants with ABSSSI, population PK analyses provided insights into the influence of these factors on tedizolid PK. In general, the results from the updated population PK analysis corroborated the PK results observed in clinical pharmacology studies, and no new conclusions are drawn from adding data from adolescent participants with ABSSSI to the previously reviewed population PK model supporting the original application. Although lower body weight is associated with higher exposure, no exposure-efficacy or exposure-safety relationships were found and body weight did not show an impact on the efficacy and safety profile in adolescent patients.

Overall, none of the evaluated intrinsic factors affected tedizolid PK in a clinically meaningful manner and, thus, no tedizolid phosphate dose adjustment based on any of these factors is warranted in adult or adolescent patients with ABSSSI.

Pharmacokinetic interaction studies

Several *in vitro* and clinical studies have been conducted to evaluate the potential for DDIs and drug-food interactions with tedizolid and tedizolid phosphate in adult ABSSSI patients. Tedizolid is primarily eliminated as a sulfate conjugate, mediated via multiple sulfotransferase isoenzymes (which minimizes the risk for clinically significant interactions with any specific isoenzyme), followed by excretion in feces. There are no reported interactions attributed to inhibition or induction of sulfotransferases.

Based on *in vitro* and *in vivo* studies, tedizolid demonstrates limited potential to perpetrate or be a victim of DDIs mediated by CYP metabolizing enzymes or major drug transporters in humans, except for BCRP in the intestine. If possible, an interruption in the treatment of the co-administered BCRP substrate drug should be considered during treatment with oral tedizolid phosphate, especially for BCRP substrates with narrow therapeutic indices. This concept is adequately captured in the SmPC for Sivextro.

The biochemical effect of nonspecific inhibition of MAO was identified in secondary pharmacology screening of tedizolid, as described in the original application. While tedizolid has MAO inhibitory activity *in vitro*, the probability of MAO inhibition *in vivo* is low at the concentrations observed after the recommended clinical dose of tedizolid phosphate in ABSSSI participants compared to the *in vitro* inhibitory concentrations.

2.3.3. Pharmacodynamics

Mechanism of action

Tedizolid phosphate is an oxazolidinone-class antibacterial prodrug of the microbiologically active molecule tedizolid (also known as TR-700), 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.

The PD studies in support of the ABSSSI indication were included in the original application. No new PD studies were conducted in support of the adolescent ABSSSI indication, which was considered acceptable by the CHMP.

2.3.4. Discussion on clinical pharmacology

A population approach was used to evaluate tedizolid PK in adolescent participants with ABSSSI by integrating PK data in healthy adult participants and participants with active bacterial infection from Phase 1 through Phase 3 adult studies and P012 (Phase 3 study in adolescent ABSSSI participants). The integrated PK data also included PK data from P026, the Phase 1 study in adolescent participants with confirmed or suspected gram-positive bacterial infection.

The results of the updated population PK analysis (with P012 data included) are consistent with the observed PK data in P026 and the conclusions drawn for the adult ABSSSI indication in the initial marketing authorization application.

The effect of age on tedizolid PK was evaluated in the population PK analysis and no meaningful change in exposure was determined across adolescents (12 to <18 years of age). As the PK in adolescents is similar to the PK in adults, no dosage adjustment is expected based on any of these factors in the adolescent population.

The similarities in the PK of tedizolid between adults and adolescents make the established profile and characterization in adults applicable to the adolescent population and support the recommendation to use the same dosage approved for adults in adolescents.

Although lower body weight is associated with higher exposure, no exposure-efficacy or exposure-safety relationships were found and body weight did not show an impact on the efficacy and safety profile in adolescent patients.

Overall, none of the evaluated intrinsic factors affected tedizolid's PK in a clinically meaningful manner and, thus, no tedizolid phosphate dose adjustment based on any of these factors is warranted in adult or adolescent patients with ABSSSI.

In terms of dose justification, favourable safety, efficacy and PK profiles in study P012 support the conclusion that the tedizolid phosphate 200 mg once daily dosage administered IV and/or orally, is appropriate in the adolescent ABSSSI patient population, as in the adult ABSSSI patient population. This conclusion is further supported by non-clinical PK/PD data and population PK modeling, together with plasma PK and PTA assessment. Study P026 also showed that the proposed dose of tedizolid phosphate is appropriate to provide efficacy in adolescent patients with ABSSSI based on similar exposure in adult ABSSSI patients after a single oral or IV dose of tedizolid phosphate 200 mg.

Testing of tedizolid in experimentally induced thigh infections in neutropenic mice determined that the fAUC/MIC ratio explained more of the variance in the exposure-response relationship than did the other candidate pharmacodynamic indices (fCmax/MIC and fTime>MIC ratio). The fAUC/MIC ratio to achieve stasis in immunocompetent mice was approximately 3, which would correspond to a total AUC/MIC ratio of approximately 15 in humans to account for human protein binding of approximately 70% to 90%. The antibacterial activity of tedizolid was demonstrated in mouse thigh infection models (both neutropenic and immunocompetent models) at plasma exposures similar to those observed in humans with the 200 mg dose of tedizolid phosphate.

Data assessed as part of the initial MAA show that a >90% probability of target attainment was achieved at the 200 mg dose of tedizolid phosphate for adult participants with ABSSSI. In P026, adolescent patients had similar AUCs compared to adults after a single IV or oral dose of 200 mg tedizolid phosphate.

Therefore, the tedizolid phosphate dosage for adolescents, 200 mg (IV or oral) once daily for 6 days, was selected based on the similar projected exposures (AUC) in adolescent participants with ABSSSI to the observed exposures in adult participants with ABSSSI that demonstrated efficacy and acceptable safety.

Using the updated population PK model and relevant demographic covariates, individual estimates of AUC0-24 on Day 1 and Day 6 (at steady state) for adolescent participants were simulated at the 200 mg dose. The exposure distribution of adolescent participants and adult participants were demonstrated to be comparable at the same dose. The PTA results indicate that tedizolid will have 100% PTA in adolescent participants across MIC values up to the susceptibility breakpoint MIC.

Based on in vivo PK/PD and PTA evidence, the tedizolid phosphate dosage of 200 mg administered IV (1-hour infusion) and/or orally once daily for 6 days is proposed for use in adolescent patients with ABSSSI.

2.3.5. Conclusions on clinical pharmacology

The following are the clinical pharmacology conclusions for tedizolid following administration of tedizolid phosphate:

- The proposed 200 mg once daily dose, administered IV or orally, provides sufficient exposure to be efficacious in adolescent patients. As tedizolid inhibits an exogenous target, the bacterial response to tedizolid is not expected to be influenced by the age of the patient. PTA analysis predicted a 100% PK/PD target attainment after IV and/or oral administration of 200 mg tedizolid phosphate once daily for 6 days to adolescent patients with ABSSSI across MIC values up to the susceptibility breakpoint.
- After oral administration of tedizolid phosphate to adolescents, tedizolid demonstrates high bioavailability, allowing switch between IV and oral dosing without a change in dose.
- No safety concerns were identified with the tedizolid phosphate 200 mg dose and no dose adjustment is required in adolescent patients, based on the similar population PK model-predicted exposure in adolescent and adult patients with ABSSSI and the lack of identified exposure-safety relationship in adolescent patients at the approved adult dosage.
- The intrinsic factors age, body weight, gender, race/ethnicity, renal impairment, and hepatic impairment, did not have a clinically meaningful effect on tedizolid PK in adults and no dose adjustments for use in adolescent patients are needed.
- *In vitro* data and Phase 1 clinical studies demonstrated tedizolid limited potential for any clinically meaningful DDIs, either as perpetrator or victim, except potential to inhibit BCRP efflux activity in the intestine after oral administration. No other extrinsic factors in adult or adolescent patients have a clinically meaningful effect on PK, as demonstrated in the population PK analysis.

The SmPC reflects that the pharmacokinetics of tedizolid were evaluated in adolescents (12 to 17 years; n=20) following administration of a single oral or IV dose of Sivextro 200 mg and in adolescents (12 to <18 years; n=91) receiving Sivextro 200 mg IV and oral every 24 hours for 6 days.

2.4. Clinical efficacy

To support the current variation, the MAH has submitted as report one study that evaluated the safety, PK and efficacy of tedizolid in adolescent participants with ABSSSI.

2.4.1. Main study

Study MK-1986-012 (P012, also known as TR701-122)

Phase 3 Study of IV to Oral 6-Day Tedizolid Phosphate Compared with 10-Day Comparator in Subjects 12 to <18 Years with cSSTI

Methods

Study Design

P012 was a randomized (3:1, tedizolid phosphate:comparator), assessor-blind, multicenter, comparator-controlled, global Phase 3 study to assess the safety and efficacy of tedizolid phosphate 200 mg IV and/or orally once daily for 6 days compared to active comparator IV and/or orally (per local standard of care) for 10 days in adolescent participants with a diagnosis of ABSSSI (due to suspected or documented gram-positive infection based on Gram stain or culture of a microbiological sample). ABSSSI comprises major cutaneous abscess, cellulitis/erysipelas, and wound infection.

The study initiated on 09 September 2015 (first subject enrolled); on 17 September 2018 the study was concluded (last patient, last visit). The choice of protocol-allowed comparator was at the investigator's discretion. The protocol-allowed IV comparators were vancomycin, linezolid (outside the EU only), clindamycin, flucloxacillin, and cefazolin. The protocol-allowed oral comparators were linezolid (outside the EU only), clindamycin, flucloxacillin, and cephalexin. Participants who received IV cefazolin could be switched to oral cephalexin only, and participants who received vancomycin (IV only) could be switched to any protocol-allowed oral comparator.

As specified in the protocol, ≥ 50% of participants were to receive assigned study treatment for a minimum 24-hour period as IV therapy before the investigator assessed for a switch to oral therapy.

For participants with major cutaneous abscess or cellulitis/erysipelas, adjunctive antibacterial therapy was prohibited; for participants with wound infection, adjunctive aztreonam (IV) and/or metronidazole (IV or orally) was allowed if the participant was determined or suspected to have an infection with gram-negative aerobic or anaerobic pathogens in addition to gram-positive pathogen(s). Gram-negative antibacterial therapy was permitted for the participants with wound infection to minimize the effect of gram-negative infection on the evaluation of efficacy. Although the risk for clinically important DDIs was low, MAOIs, tricyclic antidepressants, SSRIs, 5-HT receptor agonists, and buspirone were prohibited during the study because tedizolid has weak MAO inhibitory activity *in vitro*.

P012 was not powered for formal inferential statistical analysis of efficacy. To supplement the evaluation of the efficacy and safety of tedizolid phosphate in adolescent participants with ABSSSI, population PK modeling and simulation and PTA analyses were performed to bridge efficacy from adult to adolescent patients with ABSSSI.

The relationship of exposure to safety was also explored.

Study participants

Eligibility criteria

Individuals were eligible to participate in the study if they met all of the following criteria:

- Male or female aged 12 to less than 18 years

- Local symptoms must have started within 7 days before Study Day -1
- ABSSSI due to a suspected or documented gram-positive pathogen obtained from a baseline Gram stain or culture of a protocol-specified sample.

Participants were not eligible to participate in the study if they met any of the following criteria:

- Bacteremia, severe sepsis, or septic shock at the Screening Visit
- ABSSSI was associated with a perianal abscess, with mouth and/or perioral structures or hairline if this limited measurement of the lesion(s), or was associated with, or in close proximity to, a prosthetic device
- Infected burns, human or animal bites, vascular catheter sites, or involving thrombophlebitis
- Any rapidly evolving necrotizing process involving deep soft tissue structures
- Concomitant severe acute bacterial infection (not ABSSSI), or cellulitis/erysipelas or major cutaneous abscess with a suspected or documented infection caused by gram-negative pathogens that required an antibiotic with specific gram-negative coverage
- Participants with surgical-site infections that followed clean-contaminated surgery, contaminated surgery, surgery in a contaminated location, or that extended into the fascia or muscle layers, organs, or spaces.

Participants who received prior, short-acting therapy for the ABSSSI were eligible if prior therapy had failed. Participants with wound infections and for whom gram-negative adjunctive therapy was warranted could be enrolled if they met the other eligibility criteria.

The CHMP considered Study P012 inclusion and exclusion criteria to be acceptable.

Treatments

Study treatment is defined as tedizolid phosphate 200 mg film-coated tablets and 200 mg powder for concentrate for solution for infusion.

Comparator study drugs were provided by the site for both IV and oral administration, with selection and dose determined by local clinical practice.

The IV Comparators are vancomycin, linezolid, clindamycin, flucloxacillin, and cefazolin. The oral Comparators are linezolid, clindamycin, flucloxacillin, and cephalexin. (Note: Linezolid was allowed as a comparator outside of Europe only.)

The CHMP considered the choice of comparator study drugs active against gram positive pathogens to be acceptable.

Objectives

The primary objective of Study P012 was to compare the safety of IV and/or oral 6-day 200 mg tedizolid phosphate with 10-day Comparator in subjects 12 to <18 years with cSSTI.

The secondary objectives of this study were:

- To compare the Blinded Investigator's assessment of clinical success in the tedizolid phosphate and Comparator groups at the Test of Cure (TOC; 18 to 25 days after the first infusion) Visit in the Intent to Treat (ITT) and Clinically Evaluable at TOC (CE-TOC) Analysis Sets
- To compare the programmatic early clinical response in the tedizolid phosphate and Comparator groups at the 48-72 Hour Visit in the ITT Analysis Set
- To compare the Blinded Investigator's assessment of clinical success in the tedizolid phosphate and Comparator groups at the End of Therapy (EOT) Visit (Day 11) in the ITT and CE-EOT Analysis Sets

The following are additional objectives stated in the protocol:

- To compare the microbiological outcomes in the tedizolid phosphate and Comparator groups at the TOC Visit in the Microbiological ITT (MITT) and Microbiologically Evaluable (ME) Analysis Sets
- Subject assessment of palatability of tedizolid phosphate tablets
- The objectives of the population PK analyses are the following:
    - To characterize the PK of tedizolid in adolescent subjects, including estimation of typical PK parameters and inter-individual and residual variability
    - To estimate the effects of individual-specific covariate factors of tedizolid PK in this adolescent population
    - To provide individual metrics of tedizolid exposure for modelling probabilities of clinical success, microbiological response, or safety outcomes

Outcomes/endpoints

The following table includes the endpoints associated with the objectives:

Primary Objective	Primary Endpoint
To compare the safety of 6-day IV and/or oral tedizolid 200 mg with 10-day comparator in the Safety Analysis Set	• Percentage of participants with TEAEs in the Safety Analysis Set • Percentage of participants with substantially abnormal clinical laboratory values in the Safety Analysis Set
Secondary Objectives	**Secondary Endpoints**
To compare clinical success (per blinded investigator's assessment) in the tedizolid and comparator groups at the TOC Visit (18 to 25 days after the first dose) in the ITT and CE-TOC Analysis Sets	Percentage of participants with clinical success (per blinded investigator's assessment) at the TOC Visit in the ITT and CE-TOC Analysis Sets Note: This was the predefined primary efficacy endpoint.
To compare early clinical response in the tedizolid and comparator groups at the 48 to 72 Hour Visit in the ITT Analysis Set	Percentage of participants with programmatically determined early clinical response (≥20% reduction in lesion size) at the 48 to 72 Hour Visit in the ITT Analysis Set
To compare clinical success (per blinded investigator's assessment) in the tedizolid and comparator groups at the EOT Visit (Day 11) in the ITT and CE-EOT Analysis Sets	Percentage of participants with clinical success (per blinded investigator's assessment) at the EOT Visit in the ITT and CE-EOT Analysis Sets
Additional Objectives	**Additional Endpoints**
To compare microbiological outcomes in the tedizolid and comparator groups at the TOC Visit in the MITT and ME Analysis Sets	Percentage of participants with favorable microbiological response at the TOC Visit in the MITT and ME Analysis Sets
To assess the palatability of tedizolid phosphate tablets	Mean participant-assessed palatability score

Objectives of the population PK analyses: • To characterize the PK of tedizolid in adolescents, including typical PK parameters and inter-individual and residual variability • To estimate the effects of individual-specific covariate factors of tedizolid PK in adolescents • To provide individual metrics of tedizolid exposure for modeling probabilities of clinical success, microbiological response, or safety outcomes	All population PK data will be summarized in a separate report.
To compare change from baseline in lesion size at the 48 to 72 Hour, Day 7, EOT, and TOC Visits and the change from baseline in the assessment of signs and symptoms of ABSSSI at the EOT Visit in the tedizolid and comparator groups in the ITT Analysis Set	• Change from baseline in lesion size at the 48 to 72 Hour, Day 7, EOT, and TOC Visits in the ITT Analysis Set • Change from baseline in the assessment of signs and symptoms of ABSSSI at the EOT Visit in the ITT Analysis Set
To compare clinical success and per-pathogen clinical success (per blinded investigator's assessment) in the tedizolid and comparator groups at the TOC Visit in the MITT and ME Analysis Sets	Percentage of participants with clinical success and per-pathogen clinical success (per blinded investigator's assessment) at the TOC Visit in the MITT and ME Analysis Sets
To compare participant-reported pain in the tedizolid and comparator groups at the 48 to 72 Hour, Day 7, and EOT Visits in the ITT Analysis Set	Mean pain score at the 48 to 72 Hour, Day 7, and EOT Visits in the ITT Analysis Set

Sample size

The original protocol stated that at least 162 subjects were to be enrolled with at least 109 receiving TZD and evaluable for the safety analysis.

Amendment 6 to the protocol changed the number of subjects planned to be enrolled from 162 to 120. The number of subjects expected to receive tedizolid phosphate and evaluable for the safety analysis was changed from 109 to 86.

Randomisation

Participants with ABSSSI caused by a suspected or documented gram-positive pathogen at baseline and requiring oral or IV antibiotic therapy were randomized 3:1 (tedizolid phosphate: comparator) using an IVRS with randomization stratified by geographic region. Enrollment was stratified by geographic region to minimize the effects of differing clinical practices and epidemiology of ABSSSI.

Blinding (masking)

The efficacy evaluator and the evaluator of AE relationship (i.e. Blinded Investigator) were blinded to study treatment.

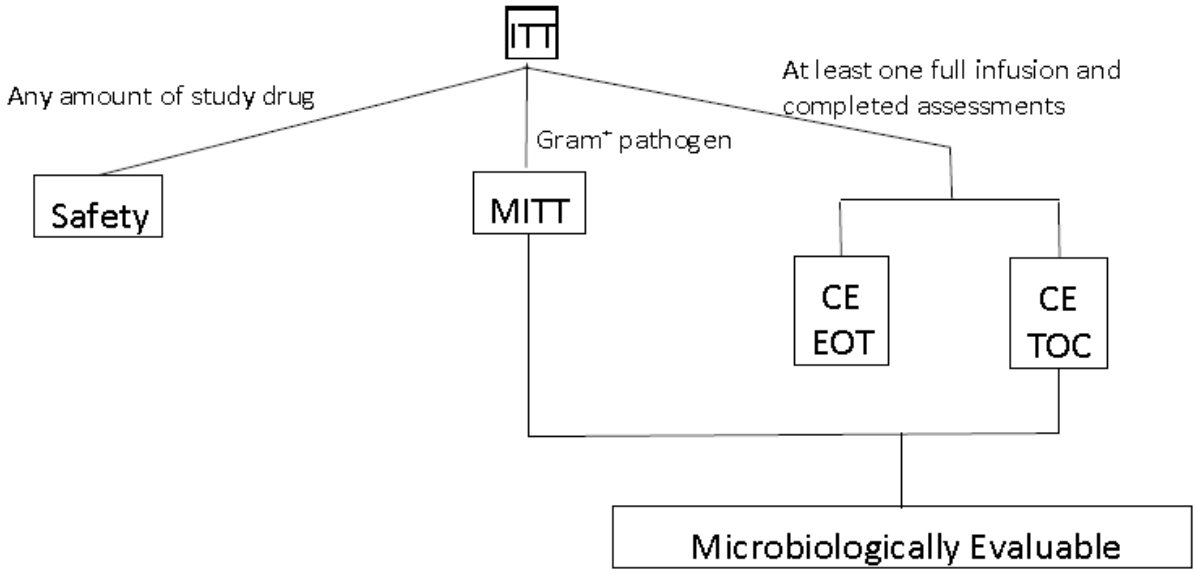
Statistical methods

Analysis sets are defined in the following table and the relationship between the 6 analysis sets is shown in the figure below.

Analysis Set	Definitions
Intent to Treat (ITT)	Data from randomized subjects
Safety	Data from randomized subjects who received any amount of study drug
Microbiological ITT (MITT)	Data from randomized subjects who have a baseline gram-positive bacterial pathogen known to cause cSSTI
Clinically Evaluable at End of Therapy (CE-EOT)	Data from randomized subjects receiving at least one full infusion of study drug who complied with the protocol with no major violations, as defined in the statistical analysis plan, and who meet the following criteria: • completed EOT Blinded Investigator's assessments • had no concomitant systemic antibiotic therapy from the first infusion of study drug through the EOT Visit that is potentially effective against the baseline pathogen except adjunctive AZ and/or MNZ in subjects with wound infections
CE-Test of Cure (CE-TOC)	Data from randomized subjects receiving at least one full infusion of study drug who complied with the protocol with no major violations, as defined in the statistical analysis plan, and who meet the following criteria: • completed EOT and TOC Blinded Investigator's assessments (unless assessed as failures at any time point before the TOC Visit) • had no concomitant systemic antibiotic therapy from first infusion of study drug through TOC Visit that is potentially effective against baseline pathogen except adjunctive AZ and/or MNZ in subjects with wound infections
Microbiologically Evaluable (ME)	Data from subjects in the MITT Analysis Set who are also in the CE-TOC Analysis Sets

Abbreviations: AZ=aztreonam; cSSTI=complicated skin and soft tissue infection; EOT=end of therapy; MNZ=metronidazole; TOC=test of cure.

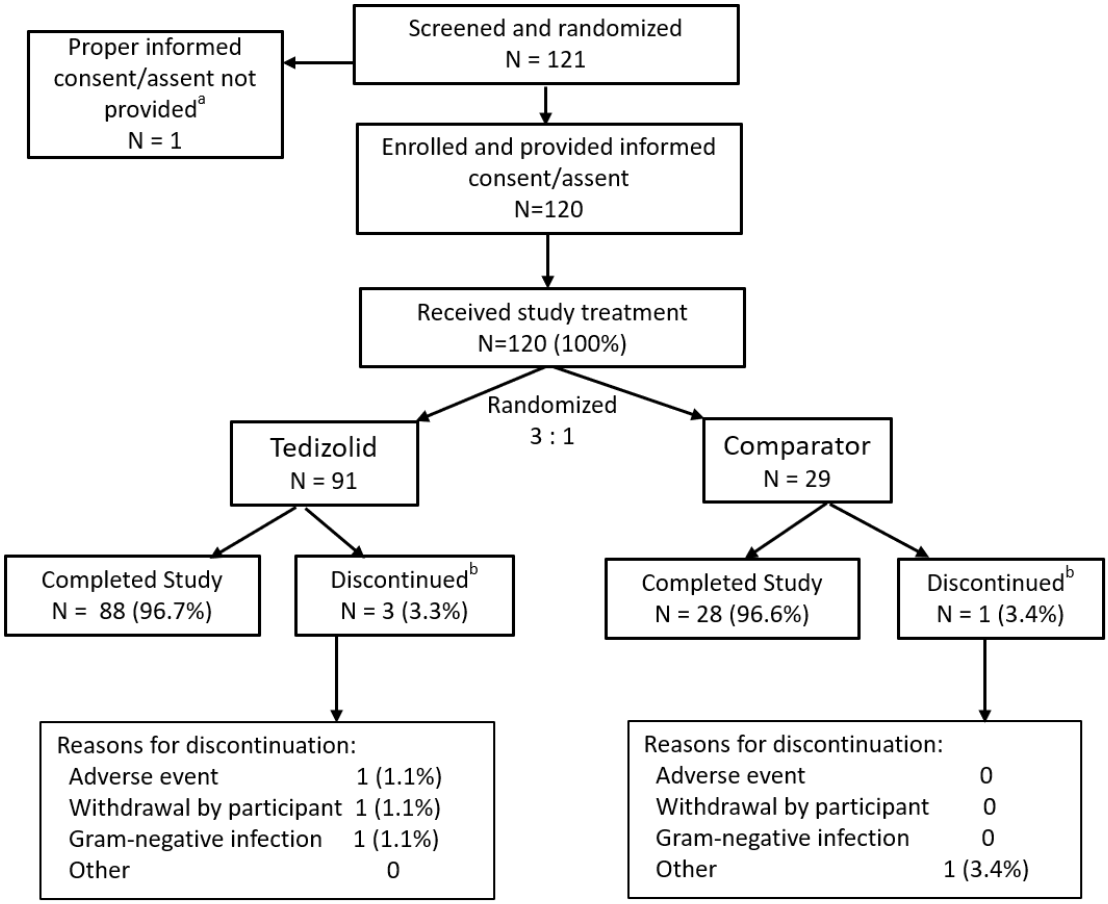
Figure 3: Analysis Sets



Abbreviations: CE=clinically evaluable; EOT= end of therapy; TOC=test of cure; ITT=intent to treat; MITT=microbiological intent to treat.

Results

Participant flow



a: One individual was randomized in error prior to the second parent's consent in a country requiring both parents' consent. This individual had no study-related procedures conducted, did not receive any study medication, and is not included in the enrolled population or in any analysis set.

b: All of these participants discontinued from both study medication and from the study. Participants are categorized by the primary reason for discontinuation.

Recruitment

Patients were recruited from 9 countries in 3 regions (North America, Europe and South Africa).

Conduct of the study

Protocol Amendments

The original protocol was issued on 09 September 2015. There were 6 amendments to the protocol.

Amendment 6 to the protocol changed the number of subjects planned to be enrolled from 162 to 120. The number of subjects expected to receive tedizolid phosphate and evaluable for the safety analysis was changed from 109 to 86.

The rationale for this change was that epidemiologic data indicate a decrease in the number of adolescents receiving treatment in acute care settings or being admitted to hospital for acute bacterial skin and skin structure infections (ABSSSI [cSSTI]). In addition, most paediatric patients receiving treatment for ABSSSI in acute care settings or hospitals are younger than those included in this study. These factors have contributed to a slower than expected rate of enrolment in this study.

To expedite study completion and provide more timely data to guide treatment for ABSSSI in children, the sample size was reduced from 162 to 120. This reduces the number of evaluable subjects in the tedizolid group from 109 to 86 subjects.

This did not substantially impact the ability to detect common or uncommon adverse events in the evaluable (safety) population. For example, with 86 evaluable subjects in the tedizolid group, the probability of observing an adverse event (AE) with an incidence of ≥ 2% will be ~82%. With the previous sample size (109 evaluable subjects in the tedizolid group), the probability of observing an AE with an incidence of ≥ 2% was similar (~89%).

Protocol Deviations

The number of important deviations (i.e., those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being) was generally low in this trial, with a lower proportion of participants in the tedizolid group than in the comparator group with such deviations. A total of 46 important protocol deviations were reported for 31 participants, primarily in the category of trial procedures.

Summary of Important Protocol Deviations
(Intent-to-Treat Analysis Set)

Type of Important Deviation Deviation Term	Tedizolid (N=91) n (%)	Comparator (N=29) n (%)	Total (N=120) n (%)
Number of Subjects with at Least One Important Deviation	20 (22.0%)	11 (37.9%)	31 (25.8%)
Informed Consent	1 (1.1%)	0 (0.0%)	1 (0.8%)
Used incorrect version of ICF.	1 (1.1%)	0 (0.0%)	1 (0.8%)
Prohibited Medications	0 (0.0%)	1 (3.4%)	1 (0.8%)
Subject took prohibited medications during the trial.	0 (0.0%)	1 (3.4%)	1 (0.8%)
Study Intervention	0 (0.0%)	1 (3.4%)	1 (0.8%)
Did not receive full course of comparator while subject was not assessed as clinical success at either EOT or TOC.	0 (0.0%)	1 (3.4%)	1 (0.8%)
Trial Procedures	19 (20.9%)	10 (34.5%)	29 (24.2%)
48-72 hour visit was performed either <48 hours or >72 hours starting from first dosing time.	3 (3.3%)	1 (3.4%)	4 (3.3%)
EOT visit was performed prior to Day 11 or after Day 13 after the first dose date.	4 (4.4%)	1 (3.4%)	5 (4.2%)
Failure to complete the pregnancy test at EOT.	6 (6.6%)	2 (6.9%)	8 (6.7%)
Failure to complete the pregnancy test prior to randomization.	2 (2.2%)	1 (3.4%)	3 (2.5%)
Lesion measurement for 48-72 hour visit was performed out of window.	3 (3.3%)	2 (6.9%)	5 (4.2%)
Missed all safety laboratory tests.	0 (0.0%)	1 (3.4%)	1 (0.8%)
Missed assessment of clinical response at EOT.	0 (0.0%)	1 (3.4%)	1 (0.8%)
Missed obtaining cSSTI site specimen at screening visit for abscess or wound infection.	1 (1.1%)	0 (0.0%)	1 (0.8%)
Missed the complete panel of blood chemistry prior to randomization.	0 (0.0%)	1 (3.4%)	1 (0.8%)
Missed the complete panel of hematology and blood chemistry at Day 7, EOT, TOC, and LFU.	0 (0.0%)	1 (3.4%)	1 (0.8%)
Missed the complete panel of hematology and blood chemistry at EOT, TOC, and LFU.	0 (0.0%)	1 (3.4%)	1 (0.8%)
Missed the complete panel of hematology prior to randomization.	5 (5.5%)	1 (3.4%)	6 (5.0%)
TOC visit was performed prior to Day 18 or after Day 25 after the first dose date.	3 (3.3%)	1 (3.4%)	4 (3.3%)

Type of Important Deviation values are representative for all deviation terms for that particular type of important deviation. Subjects may have more than one deviation per treatment group, type of important deviation, or deviation term. At each level of subject summarization, a subject is counted only once per treatment group if he/she reported one or more deviations. At each level of deviation summarization, the number of deviations includes all deviations for all subjects. Denominators for the percentages are the numbers of subjects in each treatment group.

Source: [P012MK1986: analysis-adsl; addv]

Within the category of trial procedures, most important deviations were related to study visits or a specific assessment (lesion measurement at the 48 to 72 Hour Visit) being out-of-window, or to assessments not being performed (primarily haematology, blood chemistry or pregnancy). With regard to the 3 participants with deviations of missing pregnancy tests prior to randomization, all 3 in fact had negative pregnancy tests at baseline but met criteria for important protocol deviations as follows: 2 were

randomized prior to the result being available while the third had a local laboratory result but not central laboratory confirmation. Eight participants had missing pregnancy tests at the EOT Visit due to site error; however, no pregnancy was reported during the course of the study or follow-up period.

Baseline data

The mean age of participants in both the tedizolid and comparator treatment groups (using the ITT and Safety Analysis Sets) was 14.4 years; a majority was male. A majority of participants was white, reflecting the demographic characteristics of the region where enrolment was greatest (nearly 80% of participants were enrolled in Europe, primarily Bulgaria and Georgia). Demographic characteristics were generally comparable between the treatment groups.

The more frequently identified types of ABSSSI in each treatment group were cellulitis/erysipelas (40.0% of all participants) and major cutaneous abscess (42.5% of all participants), which were seen in comparable proportions of participants in each treatment group. Wound infection was identified in a smaller proportion of participants in the tedizolid group (14.3%) than in the comparator group (27.6%).

The median surface area of the ABSSSI at baseline was comparable between the treatment groups (85.4 cm^2 in the tedizolid group and 78.0 cm^2 in the comparator group), with 7 of 91 participants in the tedizolid group and none in the comparator group having a lesion surface area ≥ 300 cm^2. A larger proportion of participants in the tedizolid group had fever at baseline. The most common location of the primary ABSSSI in each treatment group was the leg.

The most common signs and symptoms of the primary ABSSSI present at the baseline visit were erythema, localized warmth, and swelling/oedema in each of the treatment groups, with most participants reporting moderate or severe levels for each of these. Differences were seen between the treatment groups in relative proportions of participants reporting various severity levels of each of these symptoms, though these differences were not of clinical importance; the most notable was pain/tenderness on palpation, for which a majority of participants reporting this symptom in the tedizolid group reported severe pain/tenderness on palpation, while most of those reporting it in the comparator group reported moderate severity.

The most common signs or symptoms of severe infection in each treatment group were pain of at least 6 on the Wong-Baker scale (approximately 75% and 72% of participants in the tedizolid and comparator groups, respectively) and fever (56% and approximately 55% of participants, respectively); frequencies of the other signs/symptoms of severe infection were also comparable between the treatment groups.

Medical History and Concurrent Illnesses

The most frequently reported medical history condition was surgical drainage abscess (in 20% of participants overall); in each case, this was done on the day of screening/enrolment. The only other medical history term reported by ≥ 5% of participants in either treatment group was varicella. A total of 3 participants in the tedizolid group and none in the comparator group reported a history of skin/subcutaneous tissue disorders.

Prior and Concomitant Treatments

Comparable proportions of participants in each treatment group (approximately 29% and 21% in the tedizolid and comparator groups, respectively) received antibacterial therapy for the primary ABSSSI before randomization. Except for 1 participant in the comparator group, all treatments were administered systemically; the most commonly reported treatment was amoxicillin-clavulanate. The only reported

prior antibacterial treatment for gram-negative bacteria (anaerobic) was metronidazole, reported for a single participant in the tedizolid group.

Prior medications other than antibacterial therapy were reported for approximately 40% of participants overall (ITT and Safety Analysis Sets). Use of prior medications by class was generally comparable between the treatment groups with the exception of analgesics, with a larger proportion of participants in the tedizolid group reporting their use.

The most frequently reported concomitant treatment in each treatment group (≥ 10%) was ibuprofen. In the tedizolid group, the other most frequently reported concomitant treatments were sodium chloride for infusion, paracetamol, the anesthetics propofol and fentanyl, and ketorolac; in the comparator group, the other most frequently reported concomitant treatments were propofol and fentanyl.

A single participant in each treatment group received metronidazole as concomitant adjunctive therapy, as permitted by protocol, for treatment of potential anaerobic gram-negative pathogens. In addition, a single participant in the tedizolid group received paroxetine (an SSRI) before, during, and after treatment. While Amendment 5 prohibited serotonergic agents, including SSRIs and MAO inhibitors, from 2 weeks before the Screening Visit through the EOT Visit, this participant was enrolled and took part in the trial under a previous amendment; the participant reported no TEAEs.

Baseline Microbiology

The most common specimen types were needle aspiration and deep swab in both the MITT and ME Analysis Sets.

The baseline microbiological assessments of the primary infection site were comparable between the treatment groups. The majority of ABSSSI specimens in each treatment group (between 80% and 90% of samples in the MITT and ME Analysis Sets) were gram-positive cocci. On culture, a majority of specimens from the tedizolid group had growth of 4+ (heavy), while a majority of specimens from the comparator group had growth of 3+ (moderate).

Consistent with the epidemiology of ABSSSI, the most commonly isolated gram-positive pathogen at baseline in each of the treatment groups in the MITT Analysis Set was *S. aureus*, (41 [85.4%] and 14 [87.5%] in the tedizolid and comparator groups, respectively), consisting primarily of MSSA isolates. *Streptococcus pyogenes* was isolated from 9 (18.8%) and 2 (12.5%) participants in the tedizolid and comparator groups, respectively.

A single participant in the tedizolid group had an anaerobic gram-positive pathogen isolated from the baseline specimen.

Only 1 participant in the MITT Analysis Set, in the tedizolid group, had an isolate (MSSA) reported from a positive blood culture.

The majority of ABSSSI in the tedizolid group and all ABSSSI in the comparator group were monomicrobial gram-positive infections, with the remainder in the tedizolid group (approximately 15%) being polymicrobial gram-positive infections; there were no mixed (gram-positive plus gram-negative) infections in either treatment group.

Numbers analysed

Intent-to-Treat Analysis Set

The primary efficacy analysis was based on the ITT Analysis Set, which included all randomized participants. One individual was inadvertently randomized prior to conducting the screening process (consent of both parents had not been obtained in a country requiring both parents' consent). No

screening procedures were conducted, and no information was collected on this individual. The individual was excluded from the ITT Analysis Set and from all analyses; the ITT Analysis Set therefore consists of 120 participants.

Microbiological Intent-to-Treat Analysis Set

The MITT Analysis Set included all participants from the ITT Analysis Set with an ABSSSI caused by a confirmed gram-positive pathogen isolated from the baseline culture. Baseline microbiological specimens were required for all participants with abscess or wound infection; for participants with cellulitis, specimens were required only at sites where local standard of care specified specimen collection. Baseline specimens were collected from 61 participants in the tedizolid group and 22 in the comparator group in the ITT Analysis Set; of these, a total of 64 participants (48 in the tedizolid and 16 in the comparator groups) were in the MITT Analysis Set.

Clinically Evaluable at End of Therapy Analysis Set

The CE-EOT Analysis Set included all participants from the ITT Analysis Set who received at least 1 full dose of study treatment, complied with the study protocol (ie, no important protocol deviations which could confound the assessment of efficacy), completed EOT assessments, and had no concomitant systemic antibacterial therapy from the first dose of study treatment through the EOT Visit (Day 11) that was potentially effective against the baseline gram-positive pathogen. (Aztreonam and/or metronidazole were permitted for adjunctive treatment of aerobic and/or anaerobic gram-negative pathogens, respectively, in participants with wound infections.) The CE-EOT Analysis Set included a total of 114 participants (87 in the tedizolid and 27 in the comparator groups).

Clinically Evaluable at Test of Cure Analysis Set

The CE-TOC Analysis Set included all participants from the ITT Analysis Set who received at least 1 full dose of study treatment, complied with the study protocol (ie, no important protocol deviations which could confound the assessment of efficacy), completed EOT and TOC assessments (unless assessed as a failure at any time point before the TOC Visit, 18 to 25 days after the first dose), and had no concomitant systemic antibacterial therapy from the first infusion of study treatment through the TOC Visit that was potentially effective against the baseline gram-positive pathogen. (Aztreonam and/or metronidazole were permitted for adjunctive treatment of aerobic and/or anaerobic gram-negative pathogens, respectively, in participants with wound infections.) The CE-TOC Analysis Set included a total of 114 participants (87 in the tedizolid and 27 in the comparator groups).

Microbiologically Evaluable Analysis Set

The ME Analysis Set included all participants from the MITT Analysis Set who were also included in the CE-TOC Analysis Set. The ME Analysis Set included a total of 62 participants (46 in the tedizolid and 16 in the comparator groups).

Outcomes and estimation

Primary Efficacy Endpoint

The clinical success rates at the TOC Visit (18 to 25 days after first dose) were high (>93%) and comparable between the tedizolid and comparator groups in both the ITT and CE-TOC Analysis Sets. A participant assessed as a clinical failure at any point during the study was considered a clinical failure at the TOC Visit, per protocol.

Table 11-1
Summary of Blinded Investigator's Assessment of Clinical Response at the TOC Visit
(Intent-to-Treat and Clinically Evaluable at TOC Analysis Sets)

Outcome	Analysis Set	Response	Tedizolid n (%)	Comparator n (%)	Difference (%)[1]	95% Confidence Interval[1]
Clinical Response - TOC	ITT, N		91	29		
		Clinical Success	88 (96.7%)	27 (93.1%)	3.6	(-6.3, 13.5)
		95% Confidence Interval[2]	(90.7, 99.3)	(77.2, 99.2)		
		Clinical Failure or Indeterminate	3 (3.3%)	2 (6.9%)		
		Clinical Failure	1 (1.1%)	1 (3.4%)		
		Indeterminate	2 (2.2%)	1 (3.4%)		
	CE-TOC, N		87	27		
		Clinical Success	87 (100.0%)	26 (96.3%)	3.7	(-3.4, 10.8)
		95% Confidence Interval[2]	(95.8, 100.0)	(81.0, 99.9)		
		Clinical Failure	0 (0.0%)	1 (3.7%)		

Note: CE = Clinically Evaluable; ITT = Intent-to-Treat; N = Number of subjects in the specified analysis set; TOC = Test of Cure.
[1]The difference (Tedizolid minus Comparator group) in the clinical success rate and 95% confidence interval calculated using the unstratified method of Miettinen and Nurminen.
[2]An exact two-sided 95% CI determined for the rate of clinical success in each treatment group using the Clopper-Pearson method.

Source: [P012MK1986: analysis-adsl; adef]

Two sensitivity analyses of clinical success were conducted in the ITT population. The first sensitivity analysis considered all participants lost to follow-up prior to the TOC Visit or who did not have a clinical response reported for the TOC Visit as a success; these participants were considered clinical failures in the primary analysis.

Table 11-2
Summary of Blinded Investigator's Assessment of Clinical Response at the TOC Visit – Sensitivity Analysis 1
(Intent-to-Treat Analysis Set)

Outcome	Analysis Set	Response	Tedizolid n (%)	Comparator n (%)	Difference (%)[1]	95% Confidence Interval[1]
Clinical Response - TOC	ITT, N		91	29		
		Clinical Success	90 (98.9%)	28 (96.6%)	2.3	(-4.6, 9.3)
		95% Confidence Interval[2]	(94.0, 100.0)	(82.2, 99.9)		
		Clinical Failure or Indeterminate	1 (1.1%)	1 (3.4%)		
		Clinical Failure	1 (1.1%)	1 (3.4%)		
		Indeterminate	0 (0.0%)	0 (0.0%)		
	CE-TOC, N		87	27		
		Clinical Success	87 (100.0%)	26 (96.3%)	3.7	(-3.4, 10.8)
		95% Confidence Interval[2]	(95.8, 100.0)	(81.0, 99.9)		
		Clinical Failure	0 (0.0%)	1 (3.7%)		

Note: CE = Clinically Evaluable; ITT = Intent-to-Treat; N = Number of subjects in the specified analysis set; TOC = Test of Cure.
[1]The difference (Tedizolid minus Comparator group) in the clinical success rate and 95% confidence interval calculated using the unstratified method of Miettinen and Nurminen.
[2]An exact two-sided 95% CI determined for the rate of clinical success in each treatment group using the Clopper-Pearson method.
All subjects who are lost to follow up prior to the TOC visit or have missing data considered as success.

Source: [P012MK1986: analysis-adsl; adef]

The second sensitivity analysis was an adjusted analysis of the primary outcome measure in the ITT Analysis Set stratified by geographic region.

Table 11-3
Summary of Blinded Investigator's Assessment of Clinical Response at the TOC Visit – Sensitivity Analysis 2
(Intent-to-Treat Analysis Set)

Outcome	Analysis Set	Response	Tedizolid n (%)	Comparator n (%)	Difference (%)[1]	95% Confidence Interval[1]
Clinical Response - TOC	ITT, N		91	29		
		Clinical Success	88 (96.7%)	27 (93.1%)	3.6	(-4.1, 19.2)
		95% Confidence Interval[2]	(90.7, 99.3)	(77.2, 99.2)		
		Clinical Failure or Indeterminate	3 (3.3%)	2 (6.9%)		
		Clinical Failure	1 (1.1%)	1 (3.4%)		
		Indeterminate	2 (2.2%)	1 (3.4%)		
	CE-TOC, N		87	27		
		Clinical Success	87 (100.0%)	26 (96.3%)	3.7	(-3.4, 10.8)
		95% Confidence Interval[2]	(95.8, 100.0)	(81.0, 99.9)		
		Clinical Failure	0 (0.0%)	1 (3.7%)		

Note: CE = Clinically Evaluable; ITT = Intent-to-Treat; N = Number of subjects in the specified analysis set; TOC = Test of Cure.
[1]The difference (Tedizolid minus Comparator group) in the clinical success rate in ITT Analysis Set calculated using the method of Miettinen and Nurminen with stratification by geographic region. Since there are no failures in Tedizolid group in CE-TOC Analysis Set, the unadjusted method of Miettinen and Nurminen was applied.
[2]An exact two-sided 95% CI determined for the rate of clinical success in each treatment group using the Clopper-Pearson method.

Source: [P012MK1986: analysis-adsl; adef]

The results of both sensitivity analyses of clinical success in the ITT population were consistent with the primary analysis.

Secondary Efficacy Endpoints

The clinical response rates at the 48 to 72 Hour Visit were high (>92%) and comparable between the tedizolid and comparator treatment groups in the ITT Analysis Set.

Table 11-4
Summary of Early Clinical Response at 48-72 Hour Visit
(Intent-to-Treat Analysis Set)

Outcome	Analysis Set	Response	Tedizolid n (%)	Comparator n (%)	Difference (%)[1]	95% Confidence Interval[1]
Early Clinical Response at 48-72 Hour	ITT, N		91	29		
		Success/Responder	84 (92.3%)	28 (96.6%)	-4.2	(-12.9, 4.4)
		95% Confidence Interval[2]	(84.8, 96.9)	(82.2, 99.9)		
		Failure/Nonresponder or Indeterminate	7 (7.7%)	1 (3.4%)		
		Failure/Nonresponder	4 (4.4%)	0 (0.0%)		
		Indeterminate	3 (3.3%)	1 (3.4%)		

Note: ITT = Intent-to-Treat; N = Number of subjects in the specified analysis set.
[1]The difference (Tedizolid minus Comparator group) in the clinical success rate and 95% confidence interval calculated using the unstratified method of Miettinen and Nurminen.
[2]An exact two-sided 95% CI determined for the rate of clinical success in each treatment group using the Clopper-Pearson method.

Source: [P012MK1986: analysis-adsl; adef]

The clinical success rates at the EOT Visit (Day 11 + 2 days) were high (>96%) and comparable between the tedizolid and comparator groups in the ITT Analysis Set, and were 100% in both groups in the CE-EOT Analysis Set.

Table 11-5
Summary of Blinded Investigator's Assessment of Clinical Response at the EOT Visit
(Intent-to-Treat and Clinically Evaluable at EOT Analysis Sets)

Outcome	Analysis Set	Response	Tedizolid n (%)	Comparator n (%)	Difference (%)[1]	95% Confidence Interval[1]
Clinical Response - EOT	ITT, N		91	29		
		Clinical Success	88 (96.7%)	28 (96.6%)	0.2	(-7.4, 7.7)
		95% Confidence Interval[2]	(90.7, 99.3)	(82.2, 99.9)		
		Clinical Failure or Indeterminate	3 (3.3%)	1 (3.4%)		
		Clinical Failure	1 (1.1%)	0 (0.0%)		
		Indeterminate	2 (2.2%)	1 (3.4%)		
	CE-EOT, N		87	27		
		Clinical Success	87 (100.0%)	27 (100.0%)	0.0	(0.0, 0.0)
		95% Confidence Interval[2]	(95.8, 100.0)	(87.2, 100.0)		
		Clinical Failure	0 (0.0%)	0 (0.0%)		

Note: CE = Clinically Evaluable; EOT = End of Therapy; ITT = Intent-to-Treat; N = Number of subjects in the specified analysis set.
[1]The difference (Tedizolid minus Comparator group) in the clinical success rate and 95% confidence interval calculated using the unstratified method of Miettinen and Nurminen.
[2]An exact two-sided 95% CI determined for the rate of clinical success in each treatment group using the Clopper-Pearson method.

Source: [P012MK1986: analysis-adsl; adef]

Ancillary analyses

Additional efficacy analyses were conducted to support the efficacy findings of the primary and secondary efficacy outcomes.

Microbiological Outcomes (MITT and ME Analysis Sets)

The microbiological response rate (eradication or presumed eradication) at the TOC Visit was high and comparable in both the tedizolid group and the comparator group in both the MITT (92.9% and 100%, respectively) and ME Analysis Sets (>98.1% and 100%, respectively).

Table 14.2-6
Summary of Per-pathogen Microbiological Response at the TOC Visit
(Microbiological Intent-to-Treat and Microbiologically Evaluable Analysis Sets)

Outcome	Analysis Set	Response	Tedizolid n (%)	Comparator n (%)
Microbiological Response - TOC	MITT, N		56	16
		Favorable	52 (92.9%)	16 (100.0%)
		Eradication	1 (1.8%)	0 (0.0%)
		Presumed Eradication	51 (91.1%)	16 (100.0%)
		Unfavorable or Indeterminate	4 (7.1%)	0 (0.0%)
		Persistence	1 (1.8%)	0 (0.0%)
		Presumed Persistence	2 (3.6%)	0 (0.0%)
		Recurrence	0 (0.0%)	0 (0.0%)
		Indeterminate	1 (1.8%)	0 (0.0%)
	ME, N		53	16
		Favorable	52 (98.1%)	16 (100.0%)
		Eradication	1 (1.9%)	0 (0.0%)
		Presumed Eradication	51 (96.2%)	16 (100.0%)
		Unfavorable or Recurrence	1 (1.9%)	0 (0.0%)
		Persistence	1 (1.9%)	0 (0.0%)
		Presumed Persistence	0 (0.0%)	0 (0.0%)
		Recurrence	0 (0.0%)	0 (0.0%)

Note: ME = Microbiologically Evaluable; MITT = Microbiological Intent-to-Treat; N = Number of pathogens in the specified analysis set; TOC = Test of Cure.

Source: [P012MK1986: analysis-adsl; admb]

This was true whether considered on a per-pathogen or a per-participant basis. On a per-pathogen basis, response rates for *S. aureus*, the most prevalent pathogen, were 92.9% and 100% in the tedizolid and comparator group MITT Analysis Sets, respectively.

The microbiological response rates at the TOC Visit were driven by responses to *S. aureus* (specifically, MSSA). Response rates for other bacterial species could not be compared between treatment groups because of small numbers of participants infected with species other than *S. aureus*.

Changes from Baseline in Lesion Area and Symptoms (ITT Analysis Set)

Substantive decreases in median lesion surface area from baseline were seen at the 48 to 72 Hour Visit in both the tedizolid and comparator groups, with median area in each group decreasing by approximately half. Decreases from baseline in median 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 7 Visit. The median lesion surface area in the tedizolid group was 0 at the Day 7 Visit, and was 0 in both treatment groups at both the EOT and TOC Visits.

The changes in the signs and symptoms of the primary ABSSSI from the Screening Visit to the EOT Visit were comparable across treatment groups. Most signs and symptoms were absent at the EOT Visit in the majority (>89%) of participants (for whom data were available at both Screening and EOT Visits) in both treatment groups, while several signs and symptoms were absent in all participants at that visit. Among participants in the tedizolid group with signs or symptoms that were other than absent or mild at the EOT Visit, all signs and symptoms decreased in severity from the Screening Visit except for 1 participant with moderate erythema, 1 with moderate localized warmth, and 1 with severe pain, which all remain unchanged in severity, while 1 participant had swelling/edema that increased from moderate to severe at the EOT Visit. Among participants in the comparator group, all had signs or symptoms that were absent or mild at the EOT Visit.

Clinical Success Rates at TOC Visit (MITT and ME Analysis Sets)

The clinical success rates in the tedizolid and comparator groups at the TOC Visit using the MITT and ME Analysis Sets were consistent with those observed using the ITT and CE-TOC Analysis Sets.

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

Participant-reported Assessment of Pain

The mean pain intensity ratings reported by participants, based on the Wong-Baker faces pain rating scale, were comparable between treatment groups at each visit. The mean pain intensities reported at the Screening Visit in the tedizolid and comparator groups were 7.9 and 7.4 respectively, and at the EOT Visit were 0.18 and 0.00, respectively.

Rate of Relapse, Superinfection, and New Infection

One participant in the tedizolid group, with a wound infection at baseline, in the CE-TOC Analysis Set who was categorized as a clinical success at the TOC Visit was later diagnosed with relapse at the LFU Visit.

No participant in either treatment group (using the MITT Analysis Set) was diagnosed with a superinfection or a new infection at the TOC Visit.

Subgroup Analyses

Consistent with the primary analysis, in most demographic subgroup analyses the clinical success rates in the tedizolid group were comparable with those in the comparator group for the ITT and CE-TOC Analysis Sets. These subgroups were defined by standard demographic variables as well as by baseline characteristics of the primary ABSSSI, eg, diagnosis (cellulitis/erysipelas vs cutaneous abscess vs wound infection) and lesion area.

Because of the relatively small number of participants in the comparator group overall, or small participant numbers in both treatment groups in subgroups for some of these variables (eg, racial and geographic subgroups other than white and European, ABSSSI primary diagnosis of wound infection, baseline lesion areas of >150 cm^2, receipt of prior antibiotic therapy for the primary ABSSSI), comparisons should be interpreted with caution.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

To support the current variation, the MAH has submitted as report one study that evaluated the safety, PK and efficacy of tedizolid in adolescent participants with ABSSSI.

P012 was a randomized (3:1, tedizolid phosphate:comparator), assessor-blind, multicenter, comparator-controlled, global Phase 3 study to assess the safety and efficacy of tedizolid phosphate 200 mg IV and/or orally once daily for 6 days compared to active comparator IV and/or orally (per local standard of care) for 10 days in adolescent participants with a diagnosis of ABSSSI (due to suspected or documented gram-positive infection based on Gram stain or culture of a microbiological sample).

The participant flow, the baseline data and the numbers analysed were described adequately.

The inclusion and exclusion criteria are considered acceptable.

The choice of comparator study drugs active against gram positive pathogens is considered acceptable.

Efficacy data and additional analyses

Efficacy data, although exploratory, can be regarded as reassuring in subjects 12 to < 18 years with ABSSSI, with high rate of clinical success at the TOC visit, high rate of early clinical response at the 48 to 72 Hour Visit and high rate of clinical success at the EOT Visit being observed in the different sets analysed.

Additional efficacy endpoints were comparable between treatment groups in the different sets analysed.

2.4.3. Conclusions on the clinical efficacy

Overall, it is acknowledged that study P012 was not designed to substantiate clinical efficacy in subjects 12 to <18 years with ABSSSI. However, to supplement the evaluation of the efficacy of tedizolid phosphate in adolescent participants with ABSSSI, adequate analyses were performed to bridge efficacy from adult to adolescent patients with ABSSSI. The results are reassuring of an adequate efficacy of tedizolid in the treatment of ABSSSI in adolescents.

The efficacy data suggest that the recommended tedizolid doses be effective in this age group.

2.5. Clinical safety

Introduction

Tedizolid is approved in the EU for the treatment of ABSSSI in adults. Clinical safety results from a completed Phase 3 study, MK-1986-012 (P012, also known as TR701-122), that evaluated the safety and efficacy of tedizolid phosphate in adolescent participants with ABSSSI, were submitted in support of the marketing application dossier for the use of tedizolid phosphate for the treatment of ABSSSI in the adolescent population, at the same dosage approved for adults.

Additional safety data is mentioned from one study of tedizolid phosphate in adolescent participants, Study MK-1986-026 (P026, also known as TR701-111). P026 was a Phase 1 open-label, multicenter, 2-part, single-dose, parallel-design study to assess the safety and PK of tedizolid phosphate in adolescent participants who were receiving antimicrobial prophylaxis for or had a confirmed or suspected gram-positive bacterial infection and were receiving concurrent antibiotic treatment with gram-positive antibacterial activity.

Patient exposure

The safety results from study P012 were obtained from a total of 120 participants who were randomized to receive IV and/or oral tedizolid phosphate 200 mg once daily for 6 days or IV and/or oral active comparator (per local standard of care) for 10 days. All 120 participants enrolled and providing informed consent/assent in P012 received at least 1 IV and/or oral dose of tedizolid phosphate 200 mg (91 participants) or comparator (29 participants) and were included in the Safety Analysis Set.

Study P026 enrolled 20 participants, 10 received a single oral 200 mg dose of tedizolid phosphate (Part A) and 10 received a single IV 200 mg dose of tedizolid phosphate (Part B). Data from this study were used to establish that the exposure (AUC) observed at the tedizolid phosphate 200 mg (IV or oral) dose in adolescents approximates adult exposure at the same dose.

Adverse events

The incidence of TEAEs was low in both treatment groups in P012.

Table 2.7.4-absssiadol: 4
Adverse Event Summary
Adolescents (PN012) versus Adults (Pooled Phase 3 Studies)
Safety Analysis Set

	Adolescents (PN012) Tedizolid		Adolescents (PN012) Comparator		Adults (Pooled Phase 3 Studies) Tedizolid		Adults (Pooled Phase 3 Studies) Linezolid	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	91		29		1,037		1,000	
with one or more adverse events	13	(14.3)	3	(10.3)	494	(47.6)	453	(45.3)
with no adverse event	78	(85.7)	26	(89.7)	543	(52.4)	547	(54.7)
with drug-related† adverse events	3	(3.3)	1	(3.4)	235	(22.7)	248	(24.8)
with serious adverse events	1	(1.1)	0	(0.0)	30	(2.9)	25	(2.5)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.3)
with dose modification‡ due to an adverse event	1	(1.1)	0	(0.0)	24	(2.3)	19	(1.9)
who died	0	(0.0)	0	(0.0)	2	(0.2)	2	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
discontinued drug due to an adverse event	1	(1.1)	0	(0.0)	12	(1.2)	13	(1.3)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	5	(0.5)	8	(0.8)
discontinued drug due to a serious adverse event	1	(1.1)	0	(0.0)	3	(0.3)	5	(0.5)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Table only includes treatment emergent adverse events.
Pooled Phase 3 Studies include MK-1986-005, MK-1986-006, MK-1986-009, MK-1986-010.

Source: [MK1986-ISS-Y2019: adam-adsl; adae]

Most participants experienced TEAEs that were mild in severity and not considered to be related to study treatment. SAEs were reported for 1 participant in the tedizolid group; the 3 SAEs reported by the participant (pneumonia, sepsis, and venous thrombosis limb) were assessed as unrelated to study drug but the participant was discontinued from study drug and from the study due to these events so that the patient could be treated with appropriate antibiotics and other treatment. Overall, the events reported for the adolescent participants in P012 were typical for a patient population with ABSSSI. The type of TEAEs observed with tedizolid in adolescent participants in P012 was consistent with the known safety profile of tedizolid in adults with ABSSSI.

Table 2.7.4-absssiadol: 5
Subjects With Treatment-Emergent Adverse Events
(Incidence ≥ 5% in One or More Treatment Groups)
Adolescents (PN012) versus Adults (Pooled Phase 3 Studies)
Safety Analysis Set

	Adolescents (PN012) Tedizolid		Adolescents (PN012) Comparator		Adults (Pooled Phase 3 Studies) Tedizolid		Adults (Pooled Phase 3 Studies) Linezolid	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	91		29		1,037		1,000	
with one or more TEAE	13	(14.3)	3	(10.3)	494	(47.6)	453	(45.3)
with no TEAE	78	(85.7)	26	(89.7)	543	(52.4)	547	(54.7)
Gastrointestinal disorders	**1**	**(1.1)**	**1**	**(3.4)**	**150**	**(14.5)**	**194**	**(19.4)**
Nausea	0	(0.0)	1	(3.4)	74	(7.1)	99	(9.9)
General disorders and administration site conditions	**1**	**(1.1)**	**0**	**(0.0)**	**83**	**(8.0)**	**66**	**(6.6)**
Infections and infestations	**4**	**(4.4)**	**1**	**(3.4)**	**156**	**(15.0)**	**135**	**(13.5)**
Investigations	**5**	**(5.5)**	**0**	**(0.0)**	**49**	**(4.7)**	**39**	**(3.9)**
Nervous system disorders	**0**	**(0.0)**	**1**	**(3.4)**	**84**	**(8.1)**	**86**	**(8.6)**
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**87**	**(8.4)**	**69**	**(6.9)**

Every subject 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.
Pooled Phase 3 Studies include MK-1986-005, MK-1986-006, MK-1986-009, MK-1986-010.

Source: [MK1986-ISS-Y2019: adam-adsl; adae]

Most Frequently Reported Adverse Events

In P012, the proportions of participants reporting TEAEs in each treatment group were comparable. Only 2 TEAEs were reported for ≥ 2 participants in P012 (phlebitis for 3 participants and blood creatinine phosphokinase increased for 2 participants), all of which were in the tedizolid group. The phlebitis events were categorized as infusion site reactions. The 5 TEAEs in the Investigations SOC were reported for only 1 or 2 participants each (blood creatinine phosphokinase increased for 2 participants; AST increased, ALT increased, or LFT abnormal for 1 participant each), all in the tedizolid group.

Adverse Events Related to Study Intervention

The incidence of drug-related TEAEs was low in both the tedizolid and comparator treatment groups in P012. Drug-related TEAEs were reported for 4 participants. Each event was mild in severity and resolved without intervention. Three participants in the tedizolid group each experienced a single drug-related TEAE (ALT increased, AST increased, or LFT abnormal, respectively). One participant in the comparator group reported a single drug-related TEAE (nausea).

Serious adverse event/deaths/other significant events

There were no deaths due to any cause reported during the P012 study.

No drug-related SAEs were reported in P012.

A single participant in P012, in the tedizolid group, experienced 3 SAEs (pneumonia, sepsis, and venous thrombosis limb) that led to discontinuation from the study. None of the events were assessed as drug-related by the investigator.

The following TEAEs of special interest were identified for P012:

- CDI or CDAD
- Peripheral/optic neuropathy
- Lactic acidosis
- DILI
- Cardiac TEAEs associated with QT prolongation
- Potential DDIs/serotonin syndrome
- TEAEs suggestive of myelosuppression (including anaemia, neutropenia, or thrombocytopenia)

A single TEAE (anaemia), in the tedizolid group, was the only TEAE of special interest reported during the study. No TEAEs consistent with DILI were observed. Furthermore, no TEAEs suggestive of hypersensitivity or serious cutaneous reactions were reported during the study.

The TEAE of anaemia in a single participant in the tedizolid group resolved without sequelae after 8 days and was considered mild, with a decrease in haemoglobin from near the low end of the normal range at Screening (117 g/L; NR: 110 to 143) and Day 7 (113 g/L; NR: 110 to 143) to haemoglobin just below the normal range at Day 13 (106 g/L; NR:110 to143). This event was not considered to be study drug-related by the investigator. No treatment was given and no action was taken with study drug as a result of this anaemia event.

The only identified TEAE potentially suggesting infusion site reactions in adolescent participants in P012 was phlebitis. Three TEAEs of phlebitis were reported for 3 participants in the tedizolid group and none in the comparator group. Each phlebitis event involved the vein used for the infusion, as discussed in, and

began while the participant was receiving IV study medication, lasted 3 to 4 days, and resolved without sequelae. None of the events resulted in discontinuation from study medication, and all were treated with a topical anti-infective (nitrofural). The investigator in each case assessed the event as not related to study drug; each participant received several prior and concomitant (although not concurrent) medications via the same infusion site, confounding clear determination of a causal relationship with a particular medication or other factor.

In adolescent participants in P012, the frequency and severity of TEAEs suggestive of potential infusion site reactions were comparable to those observed in adults. Phlebitis was a common TEAE (≥ 1% of participants) in both adolescent and adult participants receiving IV tedizolid.

Laboratory findings

Haematology

In P012, baseline values for haematology parameters were comparable in the tedizolid and comparator groups. No clinically meaningful differences were observed between treatment groups in mean values and mean change from baseline to any visit for any parameter. Additionally, comparable proportions of participants in each treatment group experienced changes in categorized values (low/normal/high) between baseline and the EOT Visit. No clinically important differences between treatment groups were observed in results for haematology laboratory parameters based on analyses of parameters that shifted ≥2 grades and of PCS abnormal laboratory values.

Table 2.7.4-absssiadol: 6
Subjects with Potentially Clinically Significant Hematology Laboratory Findings
Adolescents (PN012) versus Adults (Pooled Phase 3 Studies)
Safety Analysis Set

		Adolescents (PN012)		Adults (Pooled Phase 3 Studies)	
		Tedizolid	Comparator	Tedizolid	Linezolid
Test Name (Unit)	Criterion	n (%)	n (%)	n (%)	n (%)
Absolute Neutrophil Count (10^9/L)	m	85	26	980	941
	< LLN	15 (17.6)	7 (26.9)	27 (2.8)	62 (6.6)
	<50% x LLN[1]	4 (4.7)	1 (3.8)	4 (0.4)	6 (0.6)
	<0.8	0	0	4 (0.4)	5 (0.5)
Hemoglobin (g/L)	m	85	26	994	957
	< LLN	4 (4.7)	0	398 (40.0)	415 (43.4)
	<75% x LLN[1]	1 (1.2)	0	34 (3.4)	33 (3.4)
	<10.1 [M], <9.0 [F]	2 (2.4)	0	40 (4.0)	32 (3.3)
Platelets (10^9/L)	m	82	26	989	950
	< LLN	3 (3.7)	0	67 (6.8)	98 (10.3)
	<75% x LLN[1]	1 (1.2)	0	21 (2.1)	36 (3.8)
	<112	1 (1.2)	0	23 (2.3)	38 (4.0)

n: Number of subjects with postbaseline test results that met the predetermined criterion.
m: Subjects with at least one post-baseline test result that are within two days after the last dose of active drug
M = male, F = female.
Laboratory values within two days after the last dose of active drug are summarized.
[1]Potentially clinically significant values are defined as <75% (<50% for absolute neutrophil count) of lower limit of normal (LLN), meeting the predetermined criteria post-baseline.
Pooled Phase 3 Studies include MK-1986-005, MK-1986-006, MK-1986-009, MK-1986-010

Source: [MK1986-ISS-Y2019: adam-adsl; adlb]

PCS abnormal values for haematology parameters are defined as <75% (<50% for ANC) of LLN; or ANC <0.8 x 103/mm3; haemoglobin <9 g/dL (females) or 10.1 g/dL (males); platelet count <112 x 103/mm3. PCS abnormal haematology values were observed for a single participant for platelets and a single participant for haemoglobin, both in the tedizolid group, and none in the comparator group; the PCS abnormal platelet and haemoglobin values were present at baseline and did not meaningfully change over the course of the study.

Adolescent participants in P012 had a similar profile of PCS abnormal haematology values for haemoglobin and platelets but a higher incidence of low and PCS low values for ANC compared to adults

in the pooled Phase 3 studies. The incidence of low and PCS low ANC values was comparable between the tedizolid and comparator groups in both adolescents and adults. In 4 of the 5 participants in P012 with a PCS low ANC, the ANC was already low or near the LLN at baseline (for 1 participant, no baseline value was available). Four of these participants were enrolled in South Africa and were black and, thus, their low ANC may reflect a benign ethnic neutropenia combined with normal reduction in neutrophil counts due to a resolving infection. Supporting this is the observation that the time course of these ANC values was not consistent with expectations regarding drug effect. An oxazolidinone-induced neutropenia would be expected to resolve shortly after study drug completion, but the ANC did not increase into the normal range through the TOC visit for 3 of the 5 participants with PCS low ANC values; this is more indicative of an alternate underlying reason for the neutropenia. The other 2 participants already had an ANC that was either substantially low (1 participant in the tedizolid group) or near the LLN (1 participant in the comparator group) at baseline.

No Grade 3 or Grade 4 haematology values, based on DAIDS version 2.0 criteria, were observed in either treatment group at the EOT Visit. Shifts in DAIDS toxicity values of ≥ 2 grades from baseline to worst postbaseline value (at any visit) were observed as follows:

• A single participant in the tedizolid group experienced a shift in lymphocytes from Grade 0 to Grade 2.

• A single participant in the comparator group experienced a shift in haemoglobin from Grade 0 to Grade 3 at the TOC visit.

In addition, a single participant in the tedizolid group experienced a 1-grade shift in haemoglobin (from Grade 2 at baseline to Grade 3 postbaseline). Postbaseline haematology values and changes from baseline in these values were comparable in the treatment groups, with no suggestion of myelosuppression in either treatment group.

Chemistry

In P012, baseline values for chemistry parameters were comparable between the treatment groups, and no clinically meaningful differences were observed between treatment groups in mean value or mean change from baseline to any visit for any given parameter. Additionally, comparable proportions of participants in each treatment group experienced changes in categorized values (low/normal/high) between baseline and the EOT Visit for most chemistry parameters.

The overall incidence of Grade 3 and Grade 4 toxicity, based on DAIDS version 2.0 criteria, was low in both treatment groups for all parameters across visits, as were shifts in categorized values of at least 2 grades from baseline to worst postbaseline value.

There were no notable differences between treatment groups in the mean and median changes in ALT, but there was a higher frequency of ALT elevation (a shift from within the NR to above the ULN between screening and EOT) in the tedizolid group (11/85 [12.9%] participants) compared with the comparator group (1/21 [4.8%] participants). A higher proportion of participants in the tedizolid group (20/86 [23.2%] participants) compared with the comparator group (3/24 [13.0%] participants) had at least a 1-grade shift from baseline to the highest postbaseline value. Most elevations were mild (1-grade shift) and resolved prior to the LFU Visit; those elevations that did not resolve prior to the LFU Visit were either first observed near the end of the study or were already elevated at baseline and varied between Grade 0 and Grade 1 elevation throughout the study. All 4 participants in the tedizolid group who had a 2- or 3-grade shift were also receiving concomitant medications such as acetaminophen or sevoflurane, for which transaminase elevations have been frequently reported. Clinically meaningful bilirubin elevations were not observed in these participants, and none discontinued study drug or the study due to these observations.

Few adolescent participants in P012 had ALT or AST shifts from normal to PCS ("substantially high") abnormal values postbaseline (for the highest postbaseline value); PCS abnormal values were observed for ALT in 4 (4.7%) participants in the tedizolid group and 1 (4.3%) participant in the comparator group and for AST in 1 (1.3%) participant in the tedizolid group and none in the comparator group.

Adolescent participants in P012 had a similar incidence of PCS abnormal ALT and AST values postbaseline (ALT 4.7% and AST 1.3%) compared with adults (ALT 3.9% and AST 2.6%). Increases in ALT and AST values of ≥2 toxicity grades from baseline to the worst postbaseline result were infrequent in both adolescent participants in P012 (ALT 4 [4.7%] participants and AST 1 [1.3%] participant) and adult participants (ALT 13 [2.1%] participants and AST 8 [1.3%] participants) in the controlled Phase 3 studies.

None of the abnormal transaminase values were associated with elevation of total bilirubin or other indicators of potential drug-induced liver injury in adolescent participants in P012 or in adult participants in the controlled Phase 3 studies. No PCS abnormal bilirubin values were observed in adolescents in P012 or adults in the controlled Phase 3 studies.

In P012, the following Grade 3 or Grade 4 values or shifts in categorized values of ≥2 grades from baseline to worst postbaseline value were considered to be of potential clinical importance:

• In the tedizolid group, 2 participants had a shift in creatinine kinase from Grade 0 to Grade 2.

• In the comparator group, a single participant had a shift in direct bilirubin value from Grade 0 to Grade 3.

One participant in the tedizolid group had a Grade 3 direct bilirubin value that was unchanged from baseline. Additional shifts of 2 grades or more were observed in both treatment groups but were not considered to be of clinical importance.

Hepatic Dysfunction

No participant in P012 had a TEAE of DILI or changes in clinical chemistry laboratory values that would be consistent with Hy's Law criteria. Few of the abnormal postbaseline ALT or AST values in P012 were considered to be clinically significant by the investigators, as there were only single AEs for ALT increased, AST increased, or LFT abnormal reported in the Hepatobiliary Disorders and Investigations SOCs. The TEAEs reported in P012 did not suggest a difference in adolescents compared to adults in the incidence of TEAEs and of drug-related TEAEs reporting clinically significant hepatic enzyme changes or LFT abnormalities.

Lactic Acidosis

Lactic acidosis is a rare but identified risk in participants who receive prolonged oxazolidinone therapy and can also be present in critically ill patients with hypotension or shock. There were no TEAEs of lactic acidosis in either treatment group.

Safety related to drug-drug interactions and other interactions

No new clinical pharmacology or preclinical pharmacodynamic studies were conducted to specifically support the adolescent ABSSSI program. There is no additional information to data in the original MA application or previously presented on the potential for DDIs that would suggest a change in the safety profile of tedizolid phosphate for adolescent use.

Serotonergic agents, including SSRIs and MAO inhibitors, were added as prohibited medications in the P012 protocol amendment 5; use was prohibited from 2 weeks before the Screening Visit through the EOT Visit. Prior to implementation of this amendment, a single participant in the tedizolid group received paroxetine (an SSRI) before, during, and after treatment, with no TEAEs reported.

The potential for DDIs has been extensively evaluated in nonclinical in vitro studies and in clinical studies in adults. Data from these studies demonstrate that tedizolid has minimal potential for cytochrome P450- and transporter-mediated DDIs in humans at clinically relevant concentrations, with the exception of BCRP. Tedizolid demonstrates a potential to inhibit efflux activity of BCRP and when coadministered orally with BCRP substrates with narrow therapeutic indices could increase their exposure and result in clinically significant interaction. Overall, based on these evaluations, the potential for systemic clinically-relevant DDIs with tedizolid is low.

Discontinuation due to adverse events

A single participant in the tedizolid group discontinued from both study drug and from the trial due to the 3 SAEs as described above.

Post-marketing experience

There has been extensive worldwide marketing experience with tedizolid phosphate, which is approved for administration in adult patients (≥ 18 years of age) with ABSSSI. Cumulatively, an estimated 220,082 patients have been exposed to tedizolid phosphate since the international birthdate (first marketing approval) of tedizolid phosphate (20-JUN-2014) through the post-marketing data cut-off date for this supplemental marketing application (07-MAR-2019). Tedizolid phosphate is currently registered and marketed in many countries and regions, including the US and EU, including the UK. There have been no records of any registration being revoked or withdrawn for safety reasons.

There have been no changes to the important identified and potential risks with tedizolid phosphate use described in product labelling based on a cumulative analysis of the post-marketing data collected since the first marketing approval of tedizolid phosphate (20-JUN-2014) through 07-MAR-2019. Likewise, there are no changes to tedizolid phosphate's potential for drug resistance, the potential for DDIs between oral tedizolid phosphate and oral BCRP substrates, or the tedizolid phosphate cardiac safety profile.

Overall, 132 SAEs have been described in a total of 259 reports from both spontaneous sources (serious and non-serious events) and non-interventional study sources (serious events only) from the date of first marketing approval (20-JUN-2014) through 07-MAR-2019. The patient's age was provided in 129 (125 in adult patients and 4 in paediatric patients) reports of the 259 reports. SARs reported thus far in the post-marketing setting are consistent with the known safety profile of tedizolid phosphate previously observed in adult clinical studies and are consistent with concurrent conditions in patients with ABSSSI. To date, no new safety signals for tedizolid phosphate have been observed based on the received post-marketing reports.

2.5.1. Discussion on clinical safety

No new clinical pharmacology or preclinical pharmacodynamic studies were conducted to specifically support the adolescent ABSSSI program. There is no additional information to data in the original MA application or previously presented on the potential for DDIs that would suggest a change in the safety profile of tedizolid phosphate for adolescent use.

Results from P012 did not identify any new or additional safety concerns for tedizolid. The identified safety concerns remain the same as those previously reported for adults with ABSSSI (C. difficile infection, development of drug-resistant bacteria, myelosuppression, or peripheral and optic neuropathy, lactic acidosis, or DDIs mediated via MAO or BCRP inhibition).

The safety profile of tedizolid phosphate in adolescent patients from P012 is comparable to that from the clinical studies and post-marketing safety experience for adult patients with ABSSSI.

2.5.2. Conclusions on clinical safety

Results from P012 indicate that Tedizolid 200 mg (IV and/or oral) once daily for 6 days was generally well tolerated. Rates of TEAEs, discontinuations of study drug due to TEAEs, and substantially abnormal laboratory results were low in both the tedizolid and comparator groups. No serious and unexpected adverse reactions were reported in this trial.
No new safety concerns for tedizolid were identified. No change in the overall safety profile of tedizolid was observed in adolescent patients with ABSSSI receiving tedizolid 200 mg IV and/or orally for 6 days.

The CHMP review of the application concluded that there were no newly identified clinically relevant safety findings in subjects 12 to < 18 years, compared with the known tedizolid safety profile in adults.

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 5.1 with this application.

The PRAC considered that the risk management plan version 5.1 was acceptable.

The CHMP endorsed the Risk Management Plan version 5.1 with the following content:

Summary of the safety concerns

Table SVIII.1:Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Myelosuppression (e.g., decreased platelets, decreased haemoglobin, decreased neutrophils)
Important potential risks	• Peripheral and optic nerve toxicity • Lactic acidosis • Emergence of drug resistance (cross-resistance to linezolid and tedizolid mediated by L3 or L4 ribosomal protein mutations)
Missing information	• Prolonged treatment >7 days • Treatment of ABSSSI in severely immunocompromised patients (e.g., patients with neutropenia, transplant recipients, HIV/AIDS) • Treatment of ABSSSI in patient populations/conditions that were under-represented in pivotal studies (e.g., elderly patients,

Table SVIII.1:Summary of Safety Concerns

Summary of safety concerns	
	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

Risk minimisation measures

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Myelosuppression (eg, decreased platelets, decreased haemoglobin, decreased neutrophils)	This item is communicated through the EU SmPC, Sections 4.2 (Posology) and 4.4	Routine (including Targeted Medical Questionnaire)
Peripheral and optic nerve toxicity	This is communicated through the EU SmPC, Section 4.4.	Routine (including Targeted Medical Questionnaire)
Lactic acidosis	This item is communicated through the EU SmPC, Section 4.4.	Routine (including Targeted Medical Questionnaire)
Emergence of Drug resistance (cross- resistance to linezolid and tedizolid mediated by L3 or L4 ribosomal protein mutations)	Section 4.4 of the SmPC communicates a warning on non-susceptible organisms. Section 5.1 of the SmPC includes statements regarding the potential mechanisms of resistance.	Additional (*In vitro* Surveillance Study)
Prolonged treatment >7 days	The SmPC (Section 4.2) outlines that the recommended dose is 200 mg once daily for 6 days. The safety and efficacy of tedizolid phosphate when administered for periods longer than 6 days have not been established.	Routine
Treatment of ABSSSI in severely immunocompromised patients (eg, patients with neutropenia, transplant recipients, HIV/AIDS)	This item is communicated through the EU SmPC, Section 4.4 on the limitations of clinical trial data.	Routine
Treatment of ABSSSI in patient populations/conditions that were under- represented in pivotal studies (e.g., elderly patients, diabetic patients, patients with acute polymicrobial infections such as major abscesses or traumatic wounds)	Section 4.4 of the SmPC contains information on the limitations of clinical trial data.	Routine

2.7. Update of the Product information

To supplement the evaluation of the efficacy and safety of tedizolid phosphate in adolescent patients with ABSSSI, population PK modeling and simulation and PTA analyses were performed to bridge efficacy from

adult to adolescent patients with ABSSSI. The relationship of exposure to safety was also studied. The data from these analyses resulted in updates to the Product Information, within the expansion of the indication for use of tedizolid phosphate to include the treatment of adolescent patients with ABSSSI.

As a consequence of the new approved indication, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

Tedizolid phosphate has been developed for the treatment of ABSSSI caused by susceptible gram-positive pathogens such as S. aureus (including MRSA and MSSA) in adults. P012 evaluated tedizolid phosphate in adolescent (12 to <18 years of age) participants with ABSSSI.

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 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 (<18 years of age) patients are generally similar across the US and EU and include empiric treatment with an antibacterial agent with broad-spectrum activity against gram-positive pathogens, including S. aureus (e.g., penicillins or macrolides). Recommended empiric treatment of ABSSSI in paediatric patients generally includes coverage for MRSA. Recommended therapeutic options for paediatric patients with ABSSSI due to MRSA are vancomycin, TMP/SMX, and doxycycline/minocycline. Ceftaroline and daptomycin are newer agents approved in the US and EU, including the UK, for use in paediatric patients with ABSSSI (including ABSSSI due to MRSA). Linezolid is approved in the US for adult and paediatric patients with ABSSSI (including ABSSSI due to MRSA) but is not approved for this indication in the EU.

Although clindamycin is an option for ABSSSI due to gram-positive bacterial infections and was an allowed comparator in P012, it is not universally effective against MRSA. The approved treatment options for adolescent patients with ABSSSI due to MRSA may be 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.

3.1.3. Main clinical studies

3.2. Favourable effects

The clinical PK, efficacy and safety data in support of this paediatric extension are derived from a randomized (3:1, tedizolid phosphate:comparator), assessor-blind, multicenter, comparator-controlled, global Phase 3 study (P012) enrolling 120 subjects 12 to < 18 years of age with a diagnosis of ABSSSI (due to suspected or documented gram-positive infection based on Gram stain or culture of a microbiological sample). The primary objective of P012 was to evaluate the safety of tedizolid in adolescent participants with ABSSSI. Evaluation of efficacy was a secondary objective and analysis of population PK, including characterization of tedizolid PK in adolescents, was an additional objective.

Efficacy data from P012 demonstrate the following:

• Tedizolid showed similar efficacy to standard-of-care comparator in a global, representative population of adolescent patients with ABSSSI.

• Microbiological outcomes were comparable in the tedizolid and comparator groups in a global, representative population of adolescent patients with ABSSSI.

Microbiology data from P012 demonstrate the following:

• Global surveillance data indicate high susceptibility rates of S. aureus and S. pyogenes to tedizolid in ABSSSI.

• The current tedizolid susceptibility breakpoints when applied to ABSSSI in adolescents with S. aureus (including MRSA and MSSA) and S. pyogenes are appropriate.

Population PK modelling and simulation and PTA analyses to bridge efficacy from adults to adolescents with ABSSSI demonstrated the following:

• Tedizolid exposures in adolescents with ABSSSI in P012 were similar to those in adults who received the same dose of tedizolid phosphate (200 mg) in Phase 2 and 3 clinical studies.

• PTA analysis demonstrated that with tedizolid phosphate 200 mg administered IV or orally, a high proportion of adolescents with ABSSSI attain the PK targets for tedizolid at an MIC of 0.5 µg/mL, and tedizolid phosphate will have 100% PTA against S. aureus at the current tedizolid breakpoint MIC.

3.3. Uncertainties and limitations about favourable effects

The favourable effects were identified from the single study P012 that included 91 participants in the tedizolid group and was not powered for inferential statistical analysis of efficacy.

Whilst it is acknowledged that this study was not designed to substantiate clinical efficacy in subjects 12 to <18 years with ABSSSI, to supplement the evaluation of the efficacy of tedizolid phosphate in adolescent participants with ABSSSI, adequate analyses were performed to bridge efficacy from adult to adolescent patients with ABSSSI. The results are reassuring of an acceptable efficacy of tedizolid in the treatment of ABSSSI in adolescents.

3.4. Unfavourable effects

Based on adult clinical trial experience, the important safety concerns to be evaluated in adolescents included myelosuppression, emergence of drug resistance, and CDAD/CDI. No new safety concerns in

any of these categories were identified in adolescents in P012. Additionally, no events suggestive of peripheral neuropathy, optic neuropathy, or lactic acidosis were observed in P012 during the 6-day duration of tedizolid phosphate treatment.

The few associated risks with tedizolid were analysed, observed to be limited, and are manageable by clinicians with routine risk minimization measures (labelling only).

3.5. Uncertainties and limitations about unfavourable effects

The unfavourable effects were identified from the single study P012 that included 91 participants in the tedizolid group. This did not, however, substantially impact the ability to detect common or uncommon adverse events in the evaluable (safety) population. The probability of observing an adverse event (AE) with an incidence of ≥ 2% was estimated to be ~82%.

3.6. Effects Table for Sivextro in treatment of ABSSSI from 12 years old and older

Effect	Short description	Unit	TZD	Control	Uncertainties / Strength of evidence
Favourable Effects					
Clinical Response	Proportion of adolescent participants in the ITT Analysis Set with clinical success (per blinded investigator's assessment) at the TOC visit	%	96.7	93.1	Data in adolescents are from a single study [a]
Microbiological response	Proportion of adolescent participants in the ME Analysis Set with microbiological response (eradication) at the TOC visit	%	97.8	100	Data in adolescents are from a single study [a]
Unfavourable Effects					
Myelosuppression	Proportion of adolescent participants in the Safety Analysis Set with anemia, thrombocytopenia or neutropenia	%	1.1	0	Data in adolescents are from a single study [a]
Myelosuppression	Proportion of adolescent participants in the Safety Analysis Set with PCS abnormal values for Hgb, Plt or ANC [b]	%	Hgb 2.4 Plt 1.2 ANC 0	Hgb 0 Plt 0 ANC 0	Data in adolescents are from a single study [a]
Hepatic safety	Proportion of adolescent participants with an AE for increased or abnormal ALT, AST and/or total bilirubin [c]	%	3.3	0	Data in adolescents are from a single study [a]
Important potential risks associated with oxazolidones, other than myelosuppression	Proportion of adolescent participants with an AE suggesting lactic acidosis, peripheral neuropathy, or optic neuropathy	%	0	0	Data in adolescents are from a single study [a]
Clinically important drug-drug interactions	Proportion of participants receiving concurrent serotonergic medications with AEs suggesting	%	0	0	Data in adolescents are from a single study [a]

Effect	Short description	Unit	TZD	Control	Uncertainties / Strength of evidence
	serotonin excess (serotonin syndrome)				

Abbreviations: AE=adverse event; ALT=alanine transaminase; ANC=absolute neutrophil count; AST=aspartate transaminase; COMP=comparator; Hgb=hemoglobin; ITT=intent-to-treat; ME=microbiologically evaluable; PCS=potentially clinically significant; Plt=platelets; PT=preferred term; TOC=test of cure; TZD=tedizolid phosphate.

Notes:

[a] P012 included 91 participants in the tedizolid group and was not powered for inferential statistical analysis of efficacy.

[b] PCS values are defined as Hgb <10.1 g/dL for males, <9 g/dL for females; ANC <0.8 × 10^9/L; and platelets <112 × 10^9/L, meeting the predetermined criteria post-baseline.

[c] PTs reviewed include: Hepatic function abnormal 0, hyperbilirubinemia 0, ALT increased 1 (1.1%). AST increased 1 (1.1%), blood bilirubin increased 0; hepatic enzyme increased 0, liver function test abnormal 1 (1.1%); transaminases increased 0.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Even if study P012 was not powered for inferential statistical analysis of efficacy, the results are reassuring of an adequate efficacy of tedizolid in the treatment of ABSSSI in adolescents.

Inclusion and exclusion criteria (complete list provided in the protocol) are considered acceptable.

The choice of comparator study drugs active against gram positive pathogens is considered acceptable.

Epidemiologic data indicate a decrease in the number of adolescents receiving treatment in acute care settings or being admitted to hospital for acute bacterial skin and skin structure infections (ABSSSI [cSSTI]). In addition, most paediatric patients receiving treatment for ABSSSI in acute care settings or hospitals are younger than those included in this study. These factors have contributed to a slower than expected rate of enrolment in this study.

To expedite study completion and provide more timely data to guide treatment for ABSSSI in children, the sample size was reduced from 162 to 120. This reduces the number of evaluable subjects in the tedizolid group from 109 to 86 subjects.

This did not substantially impact the ability to detect common or uncommon adverse events in the evaluable (safety) population. For example, with 86 evaluable subjects in the tedizolid group, the probability of observing an adverse event (AE) with an incidence of ≥ 2% will be ~82%. With the previous sample size (109 evaluable subjects in the tedizolid group), the probability of observing an AE with an incidence of ≥ 2% was similar (~89%).

No new safety concerns were identified in adolescents in this study, which could translate in comparable safety of tedizolid in adolescents and in adults treated for ABSSSI.

3.7.2. Balance of benefits and risks

Considering that the targeted tedizolid exposure in adolescents is obtained with the recommended tedizolid doses in adult subjects, the benefits provided by Sivextro outweigh the potential risks associated with it.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Sivextro is positive.

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, II and IIIB

Extension of Indication (treatment of ABSSSI in adults) to include adolescent population from 12 years old and older for Sivextro; as a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. Sections 1 and 2 of the Package Leaflet are updated in accordance.
In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.1

RMP version 5.1 has been approved with this variation.

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

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important

(pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0031/2018 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-2846-II-0035'