Amsterdam, 25 January 2024
EMA/92459/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Sivextro

International non-proprietary name: tedizolid phosphate

Procedure no.: EMA/H/C/002846/P46 010

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	27/11/2023	27/11/2023
☐	CHMP Rapporteur Assessment Report	03/01/2024	05/01/2024
☐	CHMP members comments	15/01/2024	15/01/2024
☐	Updated CHMP Rapporteur Assessment Report	18/01/2024	N/A
☒	CHMP adoption of conclusions:	25/01/2024	25/01/2024

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1. Introduction

On 16 October 2023, the MAH submitted a completed paediatric study for Sivextro (tedizolid phosphate), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview was also provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "A Phase 1, Single- and Multiple-Dose Safety and Pharmacokinetic Study of Oral and IV Tedizolid Phosphate (MK-1986) in Inpatients Under 2 Years Old", MK-1986-014 (P014) is part of a clinical development programme. The corresponding variation application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by 2024.

2.2. Information on the pharmaceutical formulation used in the study

The study used tedizolid phosphate formulated as

- sterile lyophilized powder for injection for IV administration, and
- oral suspension.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final study report for:

"*A Phase 1, Single- and Multiple-Dose Safety and Pharmacokinetic Study of Oral and IV Tedizolid Phosphate (MK-1986) in Inpatients Under 2 Years Old*", MK-1986-014 (P014).

2.3.2. Clinical study

MK-1986-014, "*A Phase 1, Single- and Multiple-Dose Safety and Pharmacokinetic Study of Oral and IV Tedizolid Phosphate (MK-1986) in Inpatients Under 2 Years Old*"

Description

"*A Phase 1, Single- and Multiple-Dose Safety and Pharmacokinetic Study of Oral and IV Tedizolid Phosphate (MK-1986) in Inpatients Under 2 Years Old*", MK-1986-014 (P014) was a non-randomized, open-label, uncontrolled, multicenter, 2-part, single- and multiple-dose intervention study to evaluate the safety and PK of tedizolid phosphate and its active metabolite tedizolid in hospitalized participants aged birth to <24 months receiving prophylaxis or treatment for a confirmed or suspected infection with gram-positive bacteria. Tedizolid phosphate was administered in 9 groups/cohorts as shown in the following table.

Group/Cohort		Age Range	Regimen	Dose[e]
Group 1	Cohort 1	28 days[a] to <6 months	Single IV infusion	First 5 participants (in Group 1): Tedizolid phosphate 3.0 mg/kg All subsequent participants (in all groups): Tedizolid phosphate 3.0 mg/kg (body weight <10 kg) or 2.5 mg/kg (body weight 10 to <30 kg)
	Cohort 2	6 months to <24 months		
Group 2	Cohort 1	Full-term neonates[b] from birth to <28 days	Single IV infusion	
	Cohort 2		Multiple IV infusions[d]	
Group 3	Cohort 1	Preterm neonates[c] from birth to <28 days	Single IV infusion	
	Cohort 2		Multiple IV infusions[d]	
Group 4		28 days[a] to <24 months	Single oral dose (Oral suspension)	
Group 5		Full-term neonates[b] from birth to <28 days		
Group 6		Preterm neonates[c] from birth to <28 days		

IA=interim analysis; IV=intravenous

[a] Preterm or full-term at birth

[b] Full-term neonate is defined as an infant born ≥37th week of gestation.

[c] Preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

[d] Multiple IV infusions administered twice daily for 3 days

[e] The first 5 participants (in Group 1) received tedizolid phosphate at a dose of 3.0 mg/kg. Based on the first IA for these 5 participants, the dose for the study was kept at 3.0 mg/kg for participants weighing <10 kg, but adjusted to 2.5 mg/kg for those weighing 10 to <30 kg. Of the 47 allocated participants, 45 received the 3.0 mg/kg dose and 2 (1 in Group 1 Cohort 2 and 1 in Group 4) received the 2.5 mg/kg dose.

Methods

Study participants

Eligible participants were male or female aged birth (≥ 26 weeks gestational age at birth) to <24 months who were hospitalized and receiving prophylaxis for or had a confirmed or suspected infection with gram-positive bacteria and receiving concurrent antibiotic treatment with gram-positive antibacterial activity, weighing ≥ 1 kg, and medically stable.

Treatments

The study interventions are presented in the following table.

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Part A	Tedizolid phosphate (MK-1986)	Refer to product labeling	Body weight <10 kg: 3 mg/kg Body weight 10 to <30 kg: 2.5 mg/kg	IV Infusion	Single dose (Group 1, and Cohort 1 of Groups 2, 3) Twice daily for 3 days (Cohort 2 of Groups 2, 3)	Test Product
Part B	Tedizolid phosphate (MK-1986)	20 mg/mL	Body weight <10 kg: 3 mg/kg Body weight 10 to <30 kg: 2.5 mg/kg	Oral	Single dose (Groups 4, 5, 6)	Test Product

IV=intravenous. Note: Dose level is the same regardless of route.

Objective(s)

Primary objective

Part A

1. To describe the single-dose pharmacokinetics (PK) of IV tedizolid phosphate and its active metabolite, tedizolid, when administered to paediatric subjects, aged 28 days to <24 months (Group 1 [Cohorts 1 and 2 combined]), full-term neonates aged birth to <28 days (Group 2), and preterm neonates aged birth to <28 days (Group 3).

2. To describe the multiple-dose PK of IV tedizolid phosphate and its active metabolite, tedizolid, when administered to full-term neonates aged birth to <28 days (Group 2), and preterm neonates aged birth to <28 days (Group 3).

Part B

3. To describe the single-dose PK of tedizolid following oral suspension of tedizolid phosphate administration to paediatric subjects aged 28 days to <24 months (Group 4), full-term neonates aged birth to <28 days (Group 5), and preterm neonates aged birth to <28 days (Group 6).

Secondary Objectives

Part A

1. To evaluate the safety and tolerability of IV tedizolid phosphate administration in paediatric subjects aged 28 days to <24 months (Group 1 [Cohorts 1 and 2 combined]), full-term neonates aged birth to <28 days (Group 2), and preterm neonates aged birth to <28 days (Group 3).

Part B

2. To evaluate the safety and tolerability of oral suspension tedizolid phosphate administration in paediatric subjects aged 28 days to <24 months (Group 4), full-term neonates aged birth to <28 days (Group 5), and preterm neonates aged birth to <28 days (Group 6).

Tertiary/Exploratory Objectives

To describe the bioavailability of tedizolid following oral suspension tedizolid phosphate administration to paediatric subjects aged 28 days to <24 months (Group 4), full-term neonates aged birth to <28 days (Group 5), and preterm neonates aged birth to <28 days (Group 6).

Outcomes/endpoints

Primary Endpoint

- For each IV group: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, apparent terminal $t_{1/2}$, CL, Vd

- For each oral group: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, apparent terminal $t_{1/2}$, CL/F, Vd/F

Secondary Endpoints

- Adverse events

Tertiary/Exploratory Endpoints

- % Bioavailability of tedizolid

Sample size

The planned enrolment was 42 participants. A total of 47 participants (includes 5 replacements) were enrolled and allocated to 1 of the 9 groups/cohorts. Of the 47 participants allocated, 40 were included in the Per Protocol (PP) population, which defined the population evaluable for PK analysis of tedizolid, and all 47 were included in the All Participants as Treated (APaT) population for safety analysis.

Randomisation and blinding (masking)

P014 was a nonrandomized, open-label study.

Statistical Methods

Safety

Summary statistics and plots will be generated for the change from baseline values at the interim analysis and the end of study, as deemed clinically appropriate.

Pharmacokinetics

IV Administration (Group 1 Cohorts 1 and 2, Group 2, and Group 3)

A non-model based geometric mean of the AUC and C_{max} of tedizolid phosphate and its active metabolite, tedizolid, after administration (5th dose or first dose on Day 3 for multiple-dose groups) will be calculated for each PK sampling scheme by age and dose (if dose adjusted at interim analysis) group.

Oral Administration (Groups 4, 5 and 6)

The AUC of tedizolid phosphate and tedizolid, administered as oral suspension will be calculated using naïve-pooled approach. Only one value for AUC will be estimated for each age group. The bioavailability will be estimated by dividing the naïve-pooled AUC from oral administrated subjects by the estimated AUC from IV administrated subjects, for each age group.

Results

Participant flow

A total of 49 individuals were screened, 2 were screen failures, and 47 participants (including 5 replacements) were allocated to 1 of 9 groups/cohorts and received study intervention. All 47 participants completed study treatment and completed the study. No participants discontinued study intervention or discontinued from the study for any reason.

Recruitment

Clinical investigator study sites were located at 30 centers in the following 5 countries: Bulgaria, Colombia, Norway, United Kingdom and United States.

Baseline data

A total of 47 participants were allocated to, and received, study treatment. Participants were allocated to each group as follows:

Regimen and Group/Cohort	Age Range	Allocated (N)	Analysis Population (N)	
			PP (PK)	APaT (Safety)
Single IV Infusion		**27**	**21**	**27**
Group 1 Cohort 1	28 days[a] to <6 months	4	4	4
Group 1 Cohort 2	6 months to <24 months	6	6	6
Group 2 Cohort 1	Full-term neonates[b] from birth to <28 days	8[d,e]	6	8
Group 3 Cohort 1	Preterm neonates[c] from birth to <28 days	9[d,e]	5	9
Multiple IV Infusions (Twice Daily for 3 Days)		**8**	**7**	**8**
Group 2 Cohort 2	Full-term neonates[b] from birth to <28 days	4	4	4
Group 3 Cohort 2	Preterm neonates[c] from birth to <28 days	4[e]	3	4
Single Oral Suspension Dose		**12**	**12**	**12**
Group 4	28 days[a] to <24 months	4	4	4
Group 5	Full-term neonates[b] from birth to <28 days	4	4	4
Group 6	Preterm neonates[c] from birth to <28 days	4	4	4
TOTAL		**47**	**40[e]**	**47**

APaT=All Participants as Treated (ie, all participants who received ≥1 dose of study intervention); BLOQ=below limit of quantitation; IV=intravenous; N=number of participants receiving the regimen or in the group/cohort; PK=pharmacokinetic(s); PP=Per Protocol

[a] Preterm or full-term at birth

[b] Full-term neonate is defined as an infant born ≥37th week of gestation.

[c] Preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

[d] 5 neonates receiving a single IV infusion (5/47 allocated participants) were replaced due to having ≥2 of their 3 PK samples BLOQ for tedizolid (2 full-term neonates in Group 2 Cohort 1 and 3 preterm neonates in Group 3 Cohort 1).

[e] 7/47 allocated participants (14.9%) were excluded from the PP population due to having ≥2 of their 3 PK samples BLOQ for tedizolid (2 full-term neonates in Group 2 Cohort 1, 4 preterm neonates in Group 3 Cohort 1, and 1 preterm neonate in Group 3 Cohort 2). Of the 7 participants excluded from the PP population, 5 were replaced (see footnote d above); and 2 were not replaced as they were enrolled after the final PK analysis and enrollment closure (1 preterm neonate in Group 3 Cohort 1 and 1 preterm neonate in Group 3 Cohort 2).

Source: [P014MK1986: adam-adsl; adex; adpc] [P014MK1986: sdtm-pc; supppc]

Mean Age (Standard Deviation):

Overall mean age (SD) across all groups was 88.8 days (165.7 days, range: 1 to 608 days).

Sex:

29 (61.7%) male, 18 (38.3%) female

Ethnicity:

26 (55.3%) not Hispanic or Latino, 20 (42.6%) Hispanic or Latino, 1 (2.1%) not reported

Race:

26 (55.3%) White; 19 (40.4%) Multiple; 1 (2.1%) American Indian or Alaska Native; 1 (2.1%) Black or African American

Pharmacokinetic results:

- Based on the first IA (Group 1 Cohorts 1 and 2 [n=5], 1 weighing <10 kg and 4 weighing 10 to <30 kg), the tedizolid phosphate doses expected to achieve comparable tedizolid exposures across the weight stratification were 3.0 mg/kg (body weight <10 kg) and 2.5 mg/kg (body weight 10 to <30 kg), twice daily for 3 days when administered as multiple IV infusions. All subsequent IAs

confirmed this dosing paradigm for the remaining 42 participants, resulting in a total of 45 participants receiving 3 mg/kg and 2 participants receiving 2.5 mg/kg tedizolid phosphate.

- Tedizolid phosphate was rapidly converted to tedizolid after IV and oral administration. NCA-based PK parameters for tedizolid phosphate (prodrug) were not estimated due to the limited number of participants having quantifiable tedizolid phosphate concentrations at ≥ 2 time points.
- The tedizolid plasma PK results in Table 2-4 of the submitted CSR were observed after IV or oral administration of tedizolid phosphate.
- Accounting for variability and imbalances in sample size across each of the age groups, tedizolid exposure (AUC, C_{max}) was generally comparable after administration of a single IV infusion or a single oral dose of tedizolid phosphate.
- The range of apparent $t_{1/2}$ was 4.17 to 7.08 hours after a single IV infusion and 3.82 to 13.4 hours after a single oral dose, supporting twice-daily dosing of tedizolid phosphate.
- Although data were more limited, steady-state tedizolid exposure ($C_{max,ss}$, $AUC_{0-12,ss}$) after multiple IV infusions of tedizolid phosphate appeared to be largely similar across full-term and preterm neonates. Tedizolid exposure after single- vs multiple-dose administration was also comparable, indicating minimal accumulation.
- In general, tedizolid exposure was largely similar after IV or oral administration, with an estimated bioavailability of 95.2%.

Tedizolid Phosphate Regimen Group/Cohort (Age Range)	**Tedizolid PK Parameter Estimates**					
Single IV infusion	N	**AUC_{0-inf}** (hr*µg/mL) GM (95% CI)[d]	N	**AUC_{0-24}** (hr*µg/mL) GM (95% CI)[d]	N	**C_{max}** (µg/mL) GM (95% CI)[d]
Group 1 Cohorts 1 and 2 (28 days[a] to <24 months)	10	14.3 (10.8, 18.9)	10	13.6 (10.2, 18.2)	10	2.19 (1.55, 3.09)
Group 2 Cohort 1 (Full-term neonates[b] birth to <28 days)	5	9.21 (2.71, 31.3)	5	8.23 (2.62, 25.9)	6	0.962 (0.489, 1.89)
Group 3 Cohort 1 (Preterm neonates[c] birth to <28 days)	3	17.8 (10.7, 29.7)	3	15.6 (10.1, 24.1)	5	1.35 (0.798, 2.29)
Multiple IV Infusions (twice daily for 3 days)	N	--	N	**$AUC_{0-12,ss}$** (hr*µg/mL)	N	**$C_{max,ss}$** (µg/mL)
Group 2 Cohort 2 (Full-term neonates[b] birth to <28 days)	--	--	1	10.5	1	1.82
Group 3 Cohort 2[d] (Preterm neonates[c] birth to <28 days)	--	--	NP	7.48	NP	1.69
Single Oral Dose	N	**AUC_{0-inf}** (hr*µg/mL)	N	**AUC_{0-24}** (hr*µg/mL)	N	**C_{max}** (µg/mL)
Group 4 (28 days[a] to <24 months)	NP	8.36	NP	7.92	NP	1.32
Group 5 (Full-term neonates[b] birth to <28 days)	NP	9.44	NP	9.25	NP	0.899
Group 6 (Preterm neonates[c] birth to <28 days)	NP	22.1	NP	14.9	NP	1.22

$AUC_{0-12,ss}$=area under the concentration-time curve from time 0 to 12 hours at steady state; AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; AUC_{0-inf}=area under the time-concentration curve extrapolated to infinity; C_{max}=maximum concentration; $C_{max,ss}$=maximum concentration at steady state; GM=geometric mean; IV=intravenous; PK=pharmacokinetic(s); N=number of participants in group or cohort; NCA=noncompartmental analysis; NP=naïve pool (ie, individual participants contributed to the PK profile but individual NCA results were not supported), wherein naïve-pooled summary tedizolid plasma PK is based on a single concentration-time profile.

[a] Preterm or full-term at birth

[b] Full-term neonate is defined as an infant born ≥37th week of gestation.

[c] Preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

[d] Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.

Number analysed

Of the 47 participants allocated, 40 were included in the PP population, which defined the population evaluable for PK analysis of tedizolid, and all 47 were included in the APaT population for safety analysis.

Efficacy results

There were no efficacy endpoints for this study.

Safety results

Overall Extent of Exposure

A total of 47 participants received at least 1 dose of tedizolid phosphate.

In Part A, 35 participants received IV tedizolid phosphate:

- 27 participants received a single IV infusion of tedizolid phosphate 3.0 mg/kg (n=26) or 2.5 mg/kg (n=1). This participant is captured in as receiving 2.5 mg/kg based on their screening weight;

however, based on their weight collected just before the start of infusion, the dose was ~3.0 mg/kg (the exact dose was 2.83 mg/kg).

- 8 participants received multiple IV infusions of tedizolid phosphate 3.0 mg/kg twice daily for 3 days (n=8).

In Part B, 12 participants received oral tedizolid phosphate in a single oral suspension dose of 3.0 mg/kg (n=11) or 2.5 mg/kg (n=1).

Summary of Adverse Events

Overall, across all groups/cohorts, AEs were reported for 8/47 (17.0%) participants. One drug-related AE (Group 6, immature granulocyte count increased) was reported after a single oral dose of tedizolid phosphate. One SAE (Group 1 Cohort 1, therapeutic product effect incomplete) and 1 ECI (Group 3 Cohort 2, anemia) were reported that were considered by the investigator to be not drug-related. No clinically meaningful changes in laboratory values or vital signs were reported. No participants discontinued study intervention or discontinued from the study for any reason, and no deaths were reported.

	Total	
	n	(%)
Participants in population	47	
with one or more adverse events	8	(17.0)
with no adverse event	39	(83.0)
with drug-relateda adverse events	1	(2.1)
with non-serious adverse events	7	(14.9)
with serious adverse events	1	(2.1)
with serious drug-related adverse events	0	(0.0)
with dose modificationb due to an adverse event	0	(0.0)
who died	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)

IV=intravenously; MD=multiple-dose; PO=orally; SD=single-dose
[a] Determined by the investigator to be related to the drug.
[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
[c] Full-term neonate is defined as an infant born ≥37th week of gestation.
[d] Preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.

Overview of Adverse Events

No AE was reported for >1 participant in any group/cohort.

	Total	
	n	(%)
Participants in population	47	
with one or more adverse events	8	(17.0)
with no adverse events	39	(83.0)
Blood and lymphatic system disorders	**1**	**(2.1)**
Anaemia	1	(2.1)
Eye disorders	**1**	**(2.1)**
Swelling of eyelid	1	(2.1)
General disorders and administration site conditions	**1**	**(2.1)**
Therapeutic product effect incomplete	1	(2.1)
Infections and infestations	**2**	**(4.3)**
Conjunctivitis	1	(2.1)
Pneumonia	1	(2.1)
Serratia sepsis	1	(2.1)
Investigations	**1**	**(2.1)**
Immature granulocyte count increased	1	(2.1)
Pregnancy, puerperium and perinatal conditions	**1**	**(2.1)**
Jaundice neonatal	1	(2.1)
Respiratory, thoracic and mediastinal disorders	**1**	**(2.1)**
Bronchopulmonary dysplasia	1	(2.1)
Skin and subcutaneous tissue disorders	**1**	**(2.1)**
Rash	1	(2.1)

IV=intravenously; MD=multiple-dose; PO=orally; SD=single-dose
Every participant is counted a single time for each applicable row and column.
[a] Full-term neonate is defined as an infant born ≥37th week of gestation.
[b] Preterm neonate is defined as a neonate born after completion of 26 weeks of gestation and before the beginning of the 37th week of gestation.
Adverse event terms are from MedDRA Version 25.1

One participant (a preterm neonate in Group 6) had 1 drug-related AE (immature granulocyte count increased) after receiving a single oral dose of tedizolid phosphate.

All AEs were mild or moderate in severity, except for 1 SAE (therapeutic product effect incomplete; n=1 in Group 1 Cohort 1) that was classified as severe and was also classified as an SAE. The participant had a slower-than-expected response to the concomitant antibiotic administered for an underlying infection.

There were no deaths reported for this study.

There were no discontinuations of study intervention due to AEs. No participant discontinued from the study for any reason.

One event of clinical interest (anaemia) was reported for 1 participant (in Group 3 Cohort 2) that was considered by the investigator to be not related to study intervention. The investigator classified the event as mild in intensity and it was reported resolved in 5 days.

The investigator considered the decrease in haemoglobin for this neonatal participant to be a clinically significant hematologic AE and, therefore, an ECI, as predefined in Section 7.2.2 of the study protocol.

The most common laboratory observation, particularly in neonates, was mild changes in haemoglobin, observed in participants with underlying sepsis and/or surgical interventions for underlying conditions. There was no apparent association of reductions in haemoglobin with exposure to tedizolid.

Assessment comment: No significant safety concern was identified.

2.3.3. Discussion on clinical aspects

No significant concerns regarding tolerability or safety were identified with the administration of tedizolid to 47 participants aged birth (≥ 26 weeks gestational age at birth) to <24 months.

3. Overall conclusion and recommendation

The results of the final report of study MK-1986-014 ("*A Phase 1, Single- and Multiple-Dose Safety and Pharmacokinetic Study of Oral and IV Tedizolid Phosphate (MK-1986) in Inpatients Under 2 Years Old*", MK-1986-014 (P014)) do not change the benefit-risk balance of tedizolid phosphate in the target population in the ongoing paediatric development programme.

☒ PAM fulfilled:

No regulatory action required.