Clinical trial results:
A Phase 1, Single-Administration Pharmacokinetic and Safety Study of Oral and IV Tedizolid Phosphate in Hospitalized Subjects 2 to <12 Years Old

Summary

EudraCT number	2015-004595-29
Trial protocol	Outside EU/EEA GB
Global end of trial date	21 December 2018

Results information

Result version number	v1
This version publication date	28 June 2019
First version publication date	28 June 2019

Trial information

Trial identification

Sponsor protocol code	MK-1986-013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02750761
WHO universal trial number (UTN)	-
Other trial identifiers	Cubist Protocol Number: TR701-120

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001379-PIP01-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study to assess the pharmacokinetics (PK) of tedizolid phosphate (MK-1986) and its active metabolite, tedizolid, and the safety of tedizolid phosphate following administration of a single intravenous (IV) or oral suspension administration to hospitalized participants ages 6 to <12 years (Group 1) and 2 to <6 years (Group 2).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Ukraine: 8
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	32
EEA total number of subjects	2

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	32
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Prior to enrollment, participants were receiving prophylaxis for or with a confirmed or suspected infection with gram-positive bacteria and receiving concurrent antibiotic treatment with gram-positive antibacterial activity.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)

Arm description:

Participants 6 to <12 years of age received a single intravenous infusion of tedizolid phosphate dosed at 5 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.

Arm type	Experimental
Investigational medicinal product name	Tedizolid phosphate
Investigational medicinal product code	
Other name	MK-1986, TR-701 FA, Sivextro
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg administered by intravenous infusion

Arm title	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)

Arm description:

Participants 6 to <12 years of age received a single intravenous infusion of tedizolid phosphate dosed at 4 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.

Arm type	Experimental
Investigational medicinal product name	Tedizolid phosphate
Investigational medicinal product code	
Other name	MK-1986, TR-701 FA, Sivextro
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 mg/kg administered by intravenous infusion

Arm title	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)

Arm description:

Participants 2 to <6 years of age received a single intravenous infusion of tedizolid phosphate dosed at 6 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.

Arm type	Experimental

Investigational medicinal product name	Tedizolid phosphate
Investigational medicinal product code	
Other name	MK-1986, TR-701 FA, Sivextro
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

6 mg/kg administered by intravenous infusion

Arm title	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)

Arm description:

Participants 2 to <6 years of age received a single intravenous infusion of tedizolid phosphate dosed at 3 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.

Arm type	Experimental
Investigational medicinal product name	Tedizolid phosphate
Investigational medicinal product code	
Other name	MK-1986, TR-701 FA, Sivextro
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg administered by intravenous infusion

Arm title	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)

Arm description:

Participants 6 to <12 years of age received a single dose of tedizolid phosphate oral suspension dosed at 4 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.

Arm type	Experimental
Investigational medicinal product name	Tedizolid phosphate
Investigational medicinal product code	
Other name	MK-1986, TR-701 FA, Sivextro
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

4 mg/kg administered orally

Arm title	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)

Arm description:

Participants 2 to <6 years of age received a single dose of tedizolid phosphate oral suspension dosed at 3 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.

Arm type	Experimental
Investigational medicinal product name	Tedizolid phosphate
Investigational medicinal product code	
Other name	MK-1986, TR-701 FA, Sivextro
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

3 mg/kg administered orally

Number of subjects in period 1	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)
Started	5	5	5
Completed	5	5	4
Not completed	0	0	1
Lost to follow-up	-	-	1

Number of subjects in period 1	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)
Started	5	6	6
Completed	5	6	6
Not completed	0	0	0
Lost to follow-up	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)
Reporting group description:	
Participants 6 to <12 years of age received a single intravenous infusion of tedizolid phosphate dosed at 5 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)
Reporting group description:	
Participants 6 to <12 years of age received a single intravenous infusion of tedizolid phosphate dosed at 4 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)
Reporting group description:	
Participants 2 to <6 years of age received a single intravenous infusion of tedizolid phosphate dosed at 6 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Reporting group description:	
Participants 2 to <6 years of age received a single intravenous infusion of tedizolid phosphate dosed at 3 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)
Reporting group description:	
Participants 6 to <12 years of age received a single dose of tedizolid phosphate oral suspension dosed at 4 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)
Reporting group description:	
Participants 2 to <6 years of age received a single dose of tedizolid phosphate oral suspension dosed at 3 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	

Reporting group values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)
Number of subjects	5	5	5
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	5	5	5
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	8.2	7.4	3.4
standard deviation	± 1.3	± 1.1	± 0.5

Gender Categorical Units: Subjects			
Female	1	2	1
Male	4	3	4
Race Units: Subjects			
Black or African American	1	2	0
Multiple	0	0	0
White	4	3	5
Ethnicity Units: Subjects			
Hispanic or Latino	3	1	2
Not Hispanic or Latino	2	4	3

Reporting group values	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)
Number of subjects	5	6	6
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	5	6	6
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	4.0	8.5	3.2
standard deviation	± 1.4	± 1.8	± 1.0
Gender Categorical Units: Subjects			
Female	3	2	4
Male	2	4	2
Race Units: Subjects			
Black or African American	0	1	0
Multiple	0	1	1
White	5	4	5
Ethnicity Units: Subjects			
Hispanic or Latino	0	3	2
Not Hispanic or Latino	5	3	4

Reporting group values	Total		
Number of subjects	32		

Age Categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	32		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	13		
Male	19		
Race Units: Subjects			
Black or African American	4		
Multiple	2		
White	26		
Ethnicity Units: Subjects			
Hispanic or Latino	11		
Not Hispanic or Latino	21		

End points

End points reporting groups

Reporting group title	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)
Reporting group description:	
Participants 6 to <12 years of age received a single intravenous infusion of tedizolid phosphate dosed at 5 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)
Reporting group description:	
Participants 6 to <12 years of age received a single intravenous infusion of tedizolid phosphate dosed at 4 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)
Reporting group description:	
Participants 2 to <6 years of age received a single intravenous infusion of tedizolid phosphate dosed at 6 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Reporting group description:	
Participants 2 to <6 years of age received a single intravenous infusion of tedizolid phosphate dosed at 3 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)
Reporting group description:	
Participants 6 to <12 years of age received a single dose of tedizolid phosphate oral suspension dosed at 4 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)
Reporting group description:	
Participants 2 to <6 years of age received a single dose of tedizolid phosphate oral suspension dosed at 3 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Subject analysis set title	Oral Administration Groups 3 & 4: Tedizolid oral 3-4 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received a single dose of tedizolid phosphate oral suspension dosed at 3-4 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Subject analysis set title	IV Administration Groups 1 & 2: Tedizolid 3-6 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received a single intravenous infusion of tedizolid phosphate dosed at 3-6 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	

Primary: Maximum observed drug concentration in plasma (Cmax) of tedizolid phosphate

End point title	Maximum observed drug concentration in plasma (Cmax) of tedizolid phosphate[1][2]
End point description:	
Cmax of tedizolid phosphate in participants ages 6 to <12 years (Group 1) and 2 to <6 years (Group 2). Tedizolid phosphate concentrations were below the lower limit of quantification in Group 3 and Group 4. Geometric mean is the geometric least squares mean. Analysis population includes all participants who received an IV dose of tedizolid phosphate and have at least one quantifiable post-administration concentration.	
End point type	Primary
End point timeframe:	
Group 1 (6 to <12 years): Day 1 immediately after infusion and at 1.5, 2, 3, 4, 6, 12, and 24 hours. Group 2 (2 to <6 years): Day 1 immediately after infusion and at 3, 6, 12, 24 and 48 hours.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports the Cmax of tedizolid phosphate for the IV dose only.

End point values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	5	4
Units: ng/mL				
geometric mean (confidence interval 95%)	76.3 (8.38 to 695)	82.4 (11.4 to 595)	710 (98.4 to 5130)	234 (25.7 to 2140)

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of tedizolid (the active metabolite)

End point title	Cmax of tedizolid (the active metabolite)[3]

End point description:

Cmax of tedizolid (active metabolite) following administration of IV or oral dose. Geometric mean is the geometric least squares mean. Analysis population includes all participants who received a dose of tedizolid phosphate and have at least one quantifiable post-administration concentration. Pharmacokinetic sampling occurred at the following time points: Group 1 (6 to <12 years): Day 1 immediately after infusion and 1.5, 2, 3, 4, 6, 12, and 24 hours; Group 2 (IV): Day 1 immediately after infusion and 3, 6, 12, 24 and 48 hours; Group 3 (6 to <12 years): Day 1 at 1, 2, 3, 4, 6, 8, 12, and 24 hours after oral dose; Group 4 (2 to <6 years): Day 1 at 3, 6, 9, 12, 24 and 48 hours after oral dose.

End point type	Primary

End point timeframe:

IV: immediately after the end of the infusion, and various time points up to 48 hours after the start of infusion as described above. Oral: at various time points up to 48 hours after the dose as described above.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	5	5
Units: ng/mL				
geometric mean (confidence interval 95%)	4960 (3440 to 7140)	4140 (2880 to 5970)	7460 (5180 to 10800)	4190 (2910 to 6030)

End point values	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: ng/mL				
geometric mean (confidence interval 95%)	2590 (1860 to 3620)	1820 (1310 to 2550)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to reach peak plasma concentration (tmax) of tedizolid phosphate

End point title	Time to reach peak plasma concentration (tmax) of tedizolid phosphate[4][5]

End point description:

Tmax of tedizolid phosphate in participants ages 6 to <12 years (Group 1) and 2 to <6 years (Group 2). Tedizolid phosphate concentrations were below the lower limit of quantification in Group 3 and Group 4. Analysis population includes all participants who received an IV dose of tedizolid phosphate and have at least one quantifiable post-administration concentration.

End point type	Primary

End point timeframe:

Group 1 (6 to <12 years): Day 1 immediately after infusion and at 1.5, 2, 3, 4, 6, 12, and 24 hours.
Group 2 (2 to <6 years): Day 1 immediately after infusion and at 3, 6, 12, 24 and 48 hours.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports the Tmax of tedizolid phosphate for the IV dose only.

End point values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	5	4
Units: Hours				
median (full range (min-max))	1.18 (1.07 to 2.07)	1.10 (1.00 to 1.33)	1.12 (1.07 to 1.17)	1.02 (1.00 to 1.05)

Statistical analyses

No statistical analyses for this end point

Primary: Tmax of tedizolid (the active metabolite)

End point title	Tmax of tedizolid (the active metabolite)[6]

End point description:

Tmax of tedizolid (active metabolite) following administration of IV or oral dose. Analysis population includes all participants who received a dose of tedizolid phosphate and have at least one quantifiable post-administration concentration. Pharmacokinetic sampling occurred at the following time points: Group 1 (6 to <12 years): Day 1 immediately after infusion and 1.5, 2, 3, 4, 6, 12, and 24 hours; Group 2 (IV): Day 1 immediately after infusion and 3, 6, 12, 24 and 48 hours; Group 3 (6 to <12 years): Day 1 at 1, 2, 3, 4, 6, 8, 12, and 24 hours after oral dose; Group 4 (2 to <6 years): Day 1 at 3, 6, 9, 12, 24 and 48 hours after oral dose.

End point type	Primary

End point timeframe:

IV: immediately after the end of the infusion, and various time points up to 48 hours after the start of infusion as described above. Oral: at various time points up to 48 hours after the dose as described above.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	5	5
Units: Hours				
median (full range (min-max))	1.18 (1.07 to 1.50)	1.10 (1.00 to 1.33)	1.12 (1.07 to 1.17)	1.00 (1.00 to 1.05)

End point values	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Hours				
median (full range (min-max))	2.53 (1.20 to 6.02)	3.08 (3.00 to 12.00)		

Statistical analyses

No statistical analyses for this end point

Primary: Area under the plasma concentration time curve (AUC) time zero to last of tedizolid phosphate

End point title	Area under the plasma concentration time curve (AUC) time zero to last of tedizolid phosphate[7][8]

End point description:

AUC of tedizolid phosphate in participants ages 6 to <12 years (Group 1) and 2 to <6 years (Group 2). Tedizolid phosphate concentrations were below the lower limit of quantification in Group 3 and Group 4. Geometric mean is the geometric least squares mean. Analysis population includes all participants who received an IV dose of tedizolid phosphate and have at least one quantifiable post-administration concentration.

End point type	Primary

End point timeframe:

Group 1 (6 to <12 years): Day 1 immediately after infusion and at 1.5, 2, 3, 4, 6, 12, and 24 hours.
Group 2 (2 to <6 years): Day 1 immediately after infusion and at 3, 6, 12, 24 and 48 hours.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports the AUC time 0 to last of tedizolid phosphate for the IV dose only.

End point values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	5	4
Units: hr*ng/mL				
geometric mean (confidence interval 95%)	64.8 (6.42 to 654)	63.6 (8.04 to 503)	433 (54.8 to 3430)	182 (18.1 to 1840)

Statistical analyses

No statistical analyses for this end point

Primary: AUC time zero to last of tedizolid (active metabolite)

End point title	AUC time zero to last of tedizolid (active metabolite)[9]

End point description:

AUC of tedizolid (active metabolite) following administration of IV or oral dose. Geometric mean is the geometric least squares mean. Analysis population includes all participants who received a dose of tedizolid phosphate and have at least one quantifiable post-administration concentration. Pharmacokinetic sampling occurred at the following time points: Group 1 (6 to <12 years): Day 1 immediately after infusion and 1.5, 2, 3, 4, 6, 12, and 24 hours; Group 2 (IV): Day 1 immediately after infusion and 3, 6, 12, 24 and 48 hours; Group 3 (6 to <12 years): Day 1 at 1, 2, 3, 4, 6, 8, 12, and 24 hours after oral dose; Group 4 (2 to <6 years): Day 1 at 3, 6, 9, 12, 24 and 48 hours after oral dose.

End point type	Primary

End point timeframe:

IV: immediately after the end of the infusion, and various time points up to 48 hours after the start of infusion as described above. Oral: at various time points up to 48 hours after the dose as described above.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	5	5
Units: hr*ng/mL				
geometric mean (confidence interval 95%)	28200 (21200 to 37600)	19700 (14800 to 26200)	26800 (20200 to 35800)	17100 (12800 to 22700)

End point values	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: hr*ng/mL				
geometric mean (confidence interval 95%)	22700 (17500 to 29500)	14600 (11200 to 18900)		

Statistical analyses

No statistical analyses for this end point

Primary: Terminal elimination half-life (t1/2) of tedizolid (active metabolite)

End point title	Terminal elimination half-life (t1/2) of tedizolid (active metabolite)[10]

End point description:

T1/2 of tedizolid (active metabolite) following administration of IV or oral dose. Analysis population includes all participants who received a dose of tedizolid phosphate and have at least one quantifiable post-administration concentration. Pharmacokinetic sampling occurred at the following time points: Group 1 (6 to <12 years): Day 1 immediately after infusion and 1.5, 2, 3, 4, 6, 12, and 24 hours; Group 2 (IV): Day 1 immediately after infusion and 3, 6, 12, 24 and 48 hours; Group 3 (6 to <12 years): Day 1 at 1, 2, 3, 4, 6, 8, 12, and 24 hours after oral dose; Group 4 (2 to <6 years): Day 1 at 3, 6, 9, 12, 24 and 48 hours after oral dose.

End point type	Primary

End point timeframe:

IV: immediately after the end of the infusion, and various time points up to 48 hours after the start of infusion as described above. Oral: at various time points up to 48 hours after the dose as described above.

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	5	5
Units: Hours				
geometric mean (geometric coefficient of variation)	5.18 (± 21.54)	4.93 (± 13.82)	5.51 (± 30.16)	5.76 (± 29.20)

End point values	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Hours				
geometric mean (geometric coefficient of variation)	6.15 (± 24.41)	6.79 (± 10.85)		

Statistical analyses

No statistical analyses for this end point

Primary: Clearance (CL) of tedizolid (active metabolite) after IV administration

End point title	Clearance (CL) of tedizolid (active metabolite) after IV administration[11][12]

End point description:

CL of IV tedizolid phosphate and its active metabolite, tedizolid, in participants ages 6 to <12 years (Group 1) and 2 to <6 years (Group 2). Analysis population includes all participants who received an IV infusion of tedizolid phosphate and have at least one quantifiable post-administration concentration.

End point type	Primary

End point timeframe:

Group 1 (6 to <12 years): Day 1 immediately after infusion and at 1.5, 2, 3, 4, 6, 12, and 24 hours.
Group 2 (2 to <6 years): Day 1 immediately after infusion and at 3, 6, 12, 24 and 48 hours.

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports the CL for the IV dose only.

End point values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	5	5
Units: mL/hr/kg				
geometric mean (geometric coefficient of variation)	4164.60 (± 36.39)	4145.73 (± 73.21)	2582.66 (± 20.64)	2461.08 (± 11.99)

Statistical analyses

No statistical analyses for this end point

Primary: Clearance (CL/F) of tedizolid (active metabolite) after oral administration

End point title	Clearance (CL/F) of tedizolid (active metabolite) after oral administration[13][14]

End point description:

CL/F of oral suspension tedizolid phosphate and its active metabolite, tedizolid, in participants ages 6 to <12 years (Group 3) and 2 to <6 years (Groups 4). Analysis population includes all participants who received an oral dose of tedizolid phosphate suspension and have at least one quantifiable post-administration concentration.

End point type	Primary

End point timeframe:

Group 3 (6 to <12 years): at 1, 2, 3, 4, 6, 8, 12, and 24 hours after the dose; Group 4 (2 to <6 years): at 3, 6, 9, 12, 24 and 48 hours after the dose

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports the CL/F for the oral dose only.

End point values	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: mL/hr/kg				
geometric mean (geometric coefficient of variation)	4073.32 (± 21.14)	2090.77 (± 50.27)		

Statistical analyses

No statistical analyses for this end point

Primary: Percent bioavailability of tedizolid

End point title	Percent bioavailability of tedizolid

End point description:

Bioavailability will be determined by comparing the area under the concentration time curve (AUC) of an oral dose vs. IV dose of tedizolid phosphate. Geometric mean is the geometric least squares mean. Analysis population includes all participants who received a dose of tedizolid phosphate and have at least one quantifiable post-administration concentration.

End point type	Primary

End point timeframe:

Ages 6 to <12 years at 1, 2, 3, 4, 6, 8, 12, and 24 hours after the dose; ages 2 to <6 years at 3, 6, 9, 12, 24 and 48 hours after the dose

End point values	Oral Administration Groups 3 & 4: Tedizolid oral 3-4 mg/kg	IV Administration Groups 1 & 2: Tedizolid 3-6 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	20		
Units: hr*ng/mL/mg/kg				
geometric mean (confidence interval 95%)	6000 (5020 to 7180)	5340 (4680 to 6100)		

Statistical analyses

Statistical analysis title	Bioavailability of Tedizolid
Statistical analysis description: Dose Normalized Oral AUC0-∞/Dose Normalized IV AUC0-∞	
Comparison groups	Oral Administration Groups 3 & 4: Tedizolid oral 3-4 mg/kg v IV Administration Groups 1 & 2: Tedizolid 3-6 mg/kg
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric mean ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.35

Secondary: Number of participants who experienced at least one adverse event

End point title	Number of participants who experienced at least one adverse event
End point description: An adverse event is defined as any untoward medical occurrence in a person administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Analysis population includes all participants who received any study drug. Participants are categorized to the actual treatment received.	
End point type	Secondary
End point timeframe: Up to 9 days	

End point values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	5	5
Units: Participants	2	1	2	0

End point values	Group 3: Tedizolid oral 4	Group 4: Tedizolid oral 3		

	mg/kg (6 to <12 years)	mg/kg (2 to <6 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who discontinued study drug due to an adverse event

End point title	Number of participants who discontinued study drug due to an adverse event

End point description:

An adverse event is defined as any untoward medical occurrence in a person administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Analysis population includes all participants who received any study drug. Participants are categorized to the actual treatment received.

End point type	Secondary

End point timeframe:

1 day

End point values	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	5	5
Units: Participants	0	0	0	0

End point values	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability of oral tedizolid phosphate suspension

End point title	Palatability of oral tedizolid phosphate suspension[15]

End point description:

Palatability of oral tedizolid phosphate suspension in participants ages 6 to <12 years (Group 3) and 2 to <6 years (Group 4). Palatability was assessed using a 5-point hedonic scale and spontaneous verbal judgment. This hedonic scale consists of 5 pictures of line drawn faces corresponding to very bad, bad, neither good nor bad, good and very good. The participant was asked to mark or point to the face to show how they felt about the taste of the study drug. Analysis population includes all participants who received an oral dose of tedizolid phosphate suspension.

End point type	Secondary

End point timeframe:

Following single oral dose

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports the palatability for the oral dose only.

End point values	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Count of participants				
Very good	0	0		
Good	0	1		
Neither good nor bad	3	2		
Bad	1	3		
Very bad	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 9 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)
Reporting group description: Participants 6 to <12 years of age received a single intravenous infusion of tedizolid phosphate dosed at 5 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)
Reporting group description: Participants 6 to <12 years of age received a single intravenous infusion of tedizolid phosphate dosed at 4 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)
Reporting group description: Participants 2 to <6 years of age received a single intravenous infusion of tedizolid phosphate dosed at 6 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)
Reporting group description: Participants 2 to <6 years of age received a single intravenous infusion of tedizolid phosphate dosed at 3 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)
Reporting group description: Participants 6 to <12 years of age received a single dose of tedizolid phosphate oral suspension dosed at 4 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	
Reporting group title	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)
Reporting group description: Participants 2 to <6 years of age received a single dose of tedizolid phosphate oral suspension dosed at 3 mg/kg of total body weight. Maximum dose is 200 mg of tedizolid phosphate.	

Serious adverse events	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Group 1 Cohort 1: Tedizolid IV 5 mg/kg (6 to <12 years)	Group 1 Cohort 2: Tedizolid IV 4 mg/kg (6 to <12 years)	Group 2 Cohort 1: Tedizolid IV 6 mg/kg (2 to <6 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	2 / 5 (40.00%)
Investigations			
Blood pressure systolic decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood pressure systolic increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Heart rate decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory rate increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Incision site swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dystonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Faeces discoloured			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Group 2 Cohort 2: Tedizolid IV 3 mg/kg (2 to <6 years)	Group 3: Tedizolid oral 4 mg/kg (6 to <12 years)	Group 4: Tedizolid oral 3 mg/kg (2 to <6 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	3 / 6 (50.00%)	1 / 6 (16.67%)
Investigations			
Blood pressure systolic decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood pressure systolic increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Heart rate decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory rate increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Incision site swelling			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Dystonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Faeces discoloured			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2016	Amendment 1: primary reason for this amendment was to define events of clinical interest, revise exclusions and concomitant medications, clarify dosing, and modify sampling time points.
25 April 2017	Amendment 2: primary reason for this amendment was to revise inclusion and exclusion criteria, and clarify events of clinical interest.
25 April 2017	Amendment 3: primary reason for this amendment was to revise exclusion criterion and disallowed concomitant medications.
14 July 2017	Amendment 4: the primary reason for this amendment was to update dosing and alternative enrollment sequences for both older and younger age groups.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported