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

Summary

EudraCT number	2014-004023-40
Trial protocol	SI BG DE CZ LT LV ES PL Outside EU/EEA
Global end of trial date	17 September 2018

Results information

Result version number	v1
This version publication date	23 March 2019
First version publication date	23 March 2019

Trial information

Trial identification

Sponsor protocol code	MK-1986-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02276482
WHO universal trial number (UTN)	-
Other trial identifiers	Cubist Protocol Number: TR701-122, Merck Protocol Number: MK-1986-012

Notes:

Sponsors

Sponsor organisation name	Cubist Pharmaceuticals LLC
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	17 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to compare the safety of intravenous (IV) and/or oral 6-day 200 mg tedizolid phosphate with 10-day comparator in participants 12 to <18 years with complicated skin and soft tissue infection (cSSTI).

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.
The following additional measure defined for this individual study was in place for the protection of trial subjects: the investigator may discontinue study medication and initiate rescue medication for the treatment of a gram negative pathogen.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 29
Country: Number of subjects enrolled	Georgia: 38
Country: Number of subjects enrolled	Latvia: 9
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Ukraine: 9
Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	South Africa: 16
Worldwide total number of subjects	120
EEA total number of subjects	47

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)	0
Adolescents (12-17 years)	120
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:

Participants included in the study were age 12 years to <18 years; had adequate venous access for intravenous (IV) administration of study drug for at least 24 hours (for participants receiving IV medication) and collection of protocol specified blood samples, and had cSSTI meeting at least 1 of the clinical syndrome definitions.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	Tedizolid Phosphate

Arm description:

Tedizolid Phosphate IV and/or oral 200 mg once per day for 6 days. Participants with gram-negative wound infection may receive aztreonam (IV) and/or metronidazole (IV or oral).

Arm type	Experimental
Investigational medicinal product name	Tedizolid Phosphate
Investigational medicinal product code	
Other name	TR701-122, MK-1986, SIVEXTRO®
Pharmaceutical forms	Infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

200 mg administered daily for 6 days

Investigational medicinal product name	Aztreonam
Investigational medicinal product code	
Other name	Azactam, Cayston
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

In countries and/or sites where aztreonam is available, adjunctive aztreonam may be initiated on Day 1 or during the first 3 days of treatment if the participant is determined or suspected to have an infection with a gram-negative aerobic pathogen.

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	
Other name	Flagyl, Metro
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Adjunctive metronidazole may be initiated on Day 1 or during the first 3 days of treatment if the participant is determined or suspected to have an infection with an anaerobic pathogen.

Arm title	Antibiotic comparator drug

Arm description:

IV and/or oral antibiotic comparator drug for 10 days. Participants with gram-negative wound infection may receive aztreonam (IV) and/or metronidazole (IV or oral).

Arm type	Active comparator
Investigational medicinal product name	Antibiotic comparator includes the following: Vancomycin, Linezolid, Clindamycin, Flucloxacillin, Cefazolin, Cephalexin.
Investigational medicinal product code	
Other name	Vancomycin: Vancocin, Firvanq, Lyphocin; Linezolid: Zyvox; Clindamycin: Cleocin; Cefazolin: Ancef, Kefzol; Cephalexin: Keflex, Zartan, Panixine, Biocef
Pharmaceutical forms	Infusion, Tablet, Capsule, Injection
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Antibiotic comparator drug, IV and/or orally for 10 days.

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	
Other name	Flagyl, Metro
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Adjunctive metronidazole may be initiated on Day 1 or during the first 3 days of treatment if the participant is determined or suspected to have an infection with an anaerobic pathogen.

Investigational medicinal product name	Aztreonam
Investigational medicinal product code	
Other name	Azactam, Cayston
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

In countries and/or sites where aztreonam is available, adjunctive aztreonam may be initiated on Day 1 or during the first 3 days of treatment if the participant is determined or suspected to have an infection with an gram-negative aerobic pathogen.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The assessor is blinded in this single-blind study.

Number of subjects in period 1	Tedizolid Phosphate	Antibiotic comparator drug
Started	91	29
Completed	88	28
Not completed	3	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
Gram-negative infection	1	-
Reason not specified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Tedizolid Phosphate
Reporting group description:	
Tedizolid Phosphate IV and/or oral 200 mg once per day for 6 days. Participants with gram-negative wound infection may receive aztreonam (IV) and/or metronidazole (IV or oral).	
Reporting group title	Antibiotic comparator drug
Reporting group description:	
IV and/or oral antibiotic comparator drug for 10 days. Participants with gram-negative wound infection may receive aztreonam (IV) and/or metronidazole (IV or oral).	

Reporting group values	Tedizolid Phosphate	Antibiotic comparator drug	Total
Number of subjects	91	29	120
Age categorical Units: Subjects			
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)	0	0	0
Adolescents (12-17 years)	91	29	120
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	14.4	14.4	
standard deviation	± 1.7	± 2.0	-
Sex: Female, Male Units: Subjects			
Female	33	12	45
Male	58	17	75
Race (NIH/OMB) Units: Subjects			
Asian	0	1	1
Black or African American	11	4	15
White	80	24	104

End points

End points reporting groups

Reporting group title	Tedizolid Phosphate

Reporting group description:

Tedizolid Phosphate IV and/or oral 200 mg once per day for 6 days. Participants with gram-negative wound infection may receive aztreonam (IV) and/or metronidazole (IV or oral).

Reporting group title	Antibiotic comparator drug

Reporting group description:

IV and/or oral antibiotic comparator drug for 10 days. Participants with gram-negative wound infection may receive aztreonam (IV) and/or metronidazole (IV or oral).

Primary: Number of Participants With Adverse Events on Tedizolid Phosphate and Comparator Drugs

End point title	Number of Participants With Adverse Events on Tedizolid Phosphate and Comparator Drugs[1]

End point description:

An adverse event (AE) refers to a treatment-emergent adverse event (TE-AE). A TE-AE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug. Analysis population consists of all randomized participants who received at least one dose of study drug.

End point type	Primary

End point timeframe:

Up to 39 days after first drug administration

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.

End point values	Tedizolid Phosphate	Antibiotic comparator drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	29		
Units: Participants	13	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Investigator's Assessment Indicating Clinical Success at Test of Cure (TOC) Visit (Intent to Treat Analysis Set)

End point title	Number of Participants with Investigator's Assessment Indicating Clinical Success at Test of Cure (TOC) Visit (Intent to Treat Analysis Set)

End point description:

Investigator’s assessment of clinical success is defined as (1) resolution or near resolution of most disease-specific signs and symptoms, (2) absence or near resolution of regional or systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal white blood cell count), if present at baseline, and (3) no new signs, symptoms, or complications attributable to the infection under study so no further antibiotic therapy is required for the treatment of the primary lesion. Analysis population consists of all randomized participants.

End point type	Secondary

End point timeframe:

TOC Visit: 18-25 days after first drug administration

End point values	Tedizolid Phosphate	Antibiotic comparator drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	29		
Units: Participants	88	27		

Statistical analyses

Statistical analysis title	Between group comparison

Statistical analysis description:

The difference (Tedizolid minus Comparator group) in the clinical success rate and 95% confidence interval calculated using the unstratified method of Miettinen and Nurminen.

Comparison groups	Antibiotic comparator drug v Tedizolid Phosphate
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentages
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	13.5

Secondary: Number of Participants with Investigator's Assessment Indicating Clinical Success at TOC Visit (Clinically Evaluable-Test of Cure [CE-TOC] Analysis Set)

End point title	Number of Participants with Investigator's Assessment Indicating Clinical Success at TOC Visit (Clinically Evaluable-Test of Cure [CE-TOC] Analysis Set)

End point description:

Investigator’s assessment of clinical success is defined as (1) resolution or near resolution of most disease-specific signs and symptoms, (2) absence or near resolution of regional or systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal white blood cell count), if present at baseline, and (3) no new signs, symptoms, or complications attributable to the infection under study so no further antibiotic therapy is required for the treatment of the primary lesion. Analysis population consists of all randomized participants who received a full dose of study treatment and completed TOC assessment.

End point type	Secondary

End point timeframe:

TOC Visit: 18-25 days after first drug administration

End point values	Tedizolid Phosphate	Antibiotic comparator drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	27		
Units: Participants	87	26		

Statistical analyses

Statistical analysis title	Between group comparison
Statistical analysis description:	
The difference (Tedizolid minus Comparator group) in the clinical success rate and 95% confidence interval calculated using the unstratified method of Miettinen and Nurminen.	
Comparison groups	Tedizolid Phosphate v Antibiotic comparator drug
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentages
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	10.8

Secondary: Number of Participants with Early Clinical Responses Measured by Lesion Reduction

End point title	Number of Participants with Early Clinical Responses Measured by Lesion Reduction
End point description:	
Early clinical response is defined as ≥20% reduction from baseline lesion area (defined as length x width of the erythema, edema, and/or induration [EEI]) at the 48-72 Hour Visit. Analysis population consists of all randomized participants.	
End point type	Secondary
End point timeframe:	
48-72 hours after first drug administration	

End point values	Tedizolid Phosphate	Antibiotic comparator drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	29		
Units: Participants	84	28		

Statistical analyses

Statistical analysis title	Between group comparison

Statistical analysis description:

The difference (Tedizolid minus Comparator group) in the clinical success rate and 95% confidence interval calculated using the unstratified method of Miettinen and Nurminen.

Comparison groups	Tedizolid Phosphate v Antibiotic comparator drug
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentages
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.9
upper limit	4.4

Secondary: Number of Participants with Investigator's Assessment Indicating Clinical Success at EOT Visit (Intent to Treat Analysis Set)

End point title	Number of Participants with Investigator's Assessment Indicating Clinical Success at EOT Visit (Intent to Treat Analysis Set)

End point description:

Investigator’s assessment of clinical success is defined as (1) resolution or near resolution of most disease specific signs and symptoms, (2) absence or near resolution of regional or systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal white blood cell count), if present at baseline, and (3) no new signs, symptoms, or complications attributable to the infection under study so no further antibiotic therapy is required for the treatment of the primary lesion. Analysis population consists of all randomized participants.

End point type	Secondary

End point timeframe:

EOT Visit: up to 13 days after first drug administration

End point values	Tedizolid Phosphate	Antibiotic comparator drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	29		
Units: Participants	88	28		

Statistical analyses

Statistical analysis title	Between group comparison

Statistical analysis description:

The difference (Tedizolid minus Comparator group) in the clinical success rate and 95% confidence interval calculated using the unstratified method of Miettinen and Nurminen.

Comparison groups	Tedizolid Phosphate v Antibiotic comparator drug
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentages
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	7.7

Secondary: Number of Participants with Investigator's Assessment Indicating Clinical Success at end of therapy (EOT) Visit (Clinically Evaluable-End of Therapy [CE-EOT] Analysis Set)

End point title	Number of Participants with Investigator's Assessment Indicating Clinical Success at end of therapy (EOT) Visit (Clinically Evaluable-End of Therapy [CE-EOT] Analysis Set)

End point description:

Investigator’s assessment of clinical success is defined as (1) resolution or near resolution of most disease specific signs and symptoms, (2)absence or near resolution of regional or systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal white blood cell count), if present at baseline, and (3) no new signs, symptoms, or complications attributable to the infection under study so no further antibiotic therapy is required for the treatment of the primary lesion. Analysis population consists of all randomized participants received a full dose of study treatment and completed EOT.

End point type	Secondary

End point timeframe:

EOT Visit: up to 13 days after first drug administration

End point values	Tedizolid Phosphate	Antibiotic comparator drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	27		
Units: Participants	87	27		

Statistical analyses

Statistical analysis title	Between group comparison

Statistical analysis description:

The difference (Tedizolid minus Comparator group) in the clinical success rate and 95% confidence interval calculated using the unstratified method of Miettinen and Nurminen.

Comparison groups	Tedizolid Phosphate v Antibiotic comparator drug
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percnetages
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Other pre-specified: Change from baseline in lesion size

End point title	Change from baseline in lesion size

End point description:

Lesion size is the area in cm^2 of erythema, edema or induration. A negative number corresponds to a decrease in lesion size. Analysis population consists of all randomized participants who received a full dose of study treatment, had a baseline value and a TOC visit value (Days 18 to 25).

End point type	Other pre-specified

End point timeframe:

Baseline and Day 25

End point values	Tedizolid Phosphate	Antibiotic comparator drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	29		
Units: cm^2				
arithmetic mean (standard deviation)				
Baseline	135.44 (± 158.66)	83.22 (± 48.55)		
TOC visit; n=88, n=28	-134.27 (± 161.18)	-82.51 (± 49.94)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Up to 39 days after first drug infusion

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Antibiotic comparator drug

Reporting group description:

IV and/or oral antibiotic comparator drug for 10 days. Participants with gram-negative wound infection may receive aztreonam (IV) and/or metronidazole (IV or oral).

Reporting group title	Tedizolid Phosphate

Reporting group description:

Tedizolid Phosphate IV and/or oral 200 mg once per day for 6 days. Participants with gram-negative wound infection may receive aztreonam (IV) and/or metronidazole (IV or oral).

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events exceeded the 5% threshold for any treatment group.

Serious adverse events	Antibiotic comparator drug	Tedizolid Phosphate	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	1 / 91 (1.10%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Venous Thrombosis Limb			
subjects affected / exposed	0 / 29 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Antibiotic comparator drug	Tedizolid Phosphate	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 29 (0.00%)	0 / 91 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2015	Amendment #1: primary reason for this amendment was to revise the study design, schedule of assessments, discontinuation of treatment, study drug, administration, sample collection, reporting of adverse events, and protocol deviations.
15 April 2016	Amendment #2: primary reason for this amendment was to revise the secondary objectives, overall study design, schedule of assessments, exclusion criteria, discontinuation of treatment, concomitant therapy rules, study drug, administration, reporting of adverse events, and handling of missing data.
27 June 2016	Amendment #3: primary reason for this amendment was to revise "IV to oral" therapy to "IV and/or oral" therapy, the inclusion/exclusion criteria, and sample collection assessment.
01 February 2017	Amendment #4: primary reason for this amendment was to revise the study design, study drug, safety samples, exclusion criteria, and discontinuation of treatment.
22 June 2017	Amendment #5: primary reason for this amendment was to revise the exclusion criteria and concomitant medications.
13 June 2018	Amendment #6: primary reason for this amendment was to revise the overall study design and the number of participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 May 2016	Global interruption was due to excursions in storage temperatures of the investigational product	23 June 2016

Notes:

Limitations and caveats

None reported