Clinical trial results:
A Phase II Open-Label, Single-arm Clinical Trial to Study the Safety, Efficacy and Pharmacokinetics of MK-3009 (Daptomycin) in Japanese Pediatric Participants Aged 1 to 17 Years with Complicated Skin and Soft Tissue Infections or Bacteremia caused by Gram-positive cocci

Summary

EudraCT number	2020-001576-15
Trial protocol	Outside EU/EEA
Global end of trial date	13 July 2020

Results information

Result version number	v1
This version publication date	25 December 2020
First version publication date	25 December 2020

Trial information

Trial identification

Sponsor protocol code	MK-3009-029

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03643952
WHO universal trial number (UTN)	-
Other trial identifiers	Japic-CTI: 184155

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)	No
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	13 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2020
Global end of trial reached?	Yes
Global end of trial date	13 July 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the safety, efficacy and pharmacokinetic (PK) parameters of daptomycin for injection in Japanese pediatric participants aged 1 to 17 years with complicated skin and soft tissue infection (cSSTI) or bacteremia caused by Gram-positive cocci.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statues 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	06 December 2018
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	Japan: 18
Worldwide total number of subjects	18
EEA total number of subjects	0

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)	5
Children (2-11 years)	9
Adolescents (12-17 years)	4
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:

This trial enrolled participants requiring treatment for cSSTI or bacteremia caused by Gram-positive cocci. Additional inclusion criteria applied.

Period 1

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

Arms

Arm title	Daptomycin-cSSTI or Bacteremia: Age 1-17

Arm description:

Participants aged 1 to 17 years old with cSSTI or bacteremia received daptomycin intravenously every 24 hours (q24 hours) for either 5-14 days for cSSTI or for 5-42 days for bacteremia

Arm type	Experimental
Investigational medicinal product name	Daptomycin for injection
Investigational medicinal product code	
Other name	MK-3009
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Once daily administration of 5, 7, 9, 10, or 12 mg/kg intravenous (IV) daptomycin infused with 25-50 mL saline over 30-60 minutes depending upon infection type and age level.

Number of subjects in period 1	Daptomycin-cSSTI or Bacteremia: Age 1-17
Started	18
Completed	17
Not completed	1
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Daptomycin-cSSTI or Bacteremia: Age 1-17
Reporting group description:	
Participants aged 1 to 17 years old with cSSTI or bacteremia received daptomycin intravenously every 24 hours (q24 hours) for either 5-14 days for cSSTI or for 5-42 days for bacteremia	

Reporting group values	Daptomycin-cSSTI or Bacteremia: Age 1-17	Total	
Number of subjects	18	18	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	5	5	
Children (2-11 years)	9	9	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender Categorical Units: Subjects			
Female	6	6	
Male	12	12	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	18	18	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	0	0	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	18	18	

End points

End points reporting groups

Reporting group title	Daptomycin-cSSTI or Bacteremia: Age 1-17
Reporting group description:	
Participants aged 1 to 17 years old with cSSTI or bacteremia received daptomycin intravenously every 24 hours (q24 hours) for either 5-14 days for cSSTI or for 5-42 days for bacteremia	
Subject analysis set title	cSSTI
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants diagnosed with complicated skin and soft tissue infection (cSSTI), known or suspected to be caused by a gram-positive cocci.	
Subject analysis set title	Bacteremia
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants had proven or probable gram-positive coccus bacteremia.	
Subject analysis set title	MITT-MRSA with cSSTI
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat (MITT)-methicillin-resistant staphylococcus aureas (MRSA) with cSSTI population consists of all enrolled participants who received at least one dose of study treatment, had a positive culture of MRSA at baseline, and were diagnosed with complicated skin and soft tissue infection (cSSTI).	
Subject analysis set title	MITT-MRSA with Bacteremia
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat (MITT)-methicillin-resistant staphylococcus aureas (MRSA) with bacteremia population consists of all enrolled participants who received at least one dose of study treatment, had a positive culture of MRSA at baseline, and were diagnosed with bacteremia.	

Primary: Percentage of Participants with an Adverse Event

End point title	Percentage of Participants with an Adverse Event[1]
End point description:	
An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event. The analysis population included all enrolled participants who received at least one dose of daptomycin. The percentage of participants who experienced an AE is reported.	
End point type	Primary
End point timeframe:	
Up to 56 days	
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: There are no between-group statistical analyses for this endpoint as the trial was conducted as a single-arm study.	

End point values	Daptomycin-cSSTI or Bacteremia: Age 1-17			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of Participants				

number (not applicable)	55.6			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants that Discontinued Study Treatment Due to an Adverse Event (AE)

End point title	Percentage of Participants that Discontinued Study Treatment Due to an Adverse Event (AE)[2]

End point description:

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event. The percentage of participants discontinued from the study due to an AE is reported. The analysis population included all enrolled participants who received at least one dose of daptomycin.

End point type	Primary

End point timeframe:

Up to 42 days

Notes:

[2] - 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: There are no between-group statistical analyses for this endpoint as the trial was conducted as a single-arm study.

End point values	Daptomycin-cSSTI or Bacteremia: Age 1-17			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Clinical Success

End point title	Percentage of Participants with Clinical Success

End point description:

The investigator's assessment of clinical response was conducted at the Test of Cure (TOC) visit, approximately 7 days after the completion of therapy. Clinical success was defined as 1) resolution of clinically significant signs and symptoms associated with admission infection and no further antibiotic therapy required, OR 2) partial resolution of clinical signs or symptoms of infection with no further antibiotic therapy required. The percentage of participants with clinical success is reported in the MITT-MRSA with cSSTI and MITT-MRSA with bacteremia populations--all enrolled participants who received at least one dose of study treatment, had a positive culture of MRSA at baseline, and were diagnosed with either cSSTI or bacteremia, respectively.

End point type	Secondary

End point timeframe:

Up to 10 days following end of treatment (Up to 52 days)

End point values	MITT-MRSA with cSSTI	MITT-MRSA with Bacteremia		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	1		
Units: Percentage of participants				
number (confidence interval 95%)	85.7 (42.1 to 99.6)	100 (2.5 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Subject-Level Microbiological Success

End point title	Percentage of Participants with Subject-Level Microbiological Success

End point description:

The investigator's assessment of subject-level microbiological response was conducted at the Test of Cure (TOC) visit, approximately 7 days after the completion of therapy. Subject-level microbiological success is defined as 1) absence or presumed absence of all baseline infecting pathogens AND 2) no gram-positive superinfection or gram-positive new infection. The percentage of participants with subject-level microbiological success is reported in the MITT-MRSA with cSSTI and MITT-MRSA with bacteremia populations--all enrolled participants who received at least one dose of study treatment, had a positive culture of MRSA at baseline, and were diagnosed with either cSSTI or bacteremia, respectively.

End point type	Secondary

End point timeframe:

Up to 10 days following EOT (up to 52 days)

End point values	MITT-MRSA with cSSTI	MITT-MRSA with Bacteremia		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	1		
Units: Percentage of Participants				
number (confidence interval 95%)	71.4 (29.0 to 96.3)	100 (2.5 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Time Curve from Time 0 to 24 Hours (AUC0-24) Parameters

End point title	Area Under the Concentration Time Curve from Time 0 to 24 Hours (AUC0-24) Parameters

End point description:

Plasma samples were collected at 5 timepoints on day 3 of daptomycin treatment. The analysis population included all enrolled participants who received at least 3 consecutive IV infusions of study treatment, had at least 1 pharmacokinetic (PK) sample following study drug administration, and did not have any protocol violations affecting the PK profile. The mean of the AUC0-24 (µg·hr/mL) is presented in each age category in participants with cSSTI. In participants with bacteremia, the individual AUC0-24 (µg·hr/mL) is presented.

End point type	Secondary

End point timeframe:

On Day 3 of study drug administration- pre dose, 15 minutes, 1 hour, 4 hours, and 12 hours after the end of infusion.

End point values	cSSTI	Bacteremia		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	3		
Units: µg·hr/mL				
arithmetic mean (standard deviation)				
Age Category 1-<2 (n=3, 1)	574 (± 99.1)	502 (± 0)		
Age Category 2-6 (n=3, 0)	431 (± 53.6)	0 (± 0)		
Age Category 7-11 (n=5, 1)	409 (± 143)	599 (± 0)		
Age Category 12-17 (n=3, 1)	316 (± 18.2)	422 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Maximum Concentration (Cmax)

End point title	Mean Maximum Concentration (Cmax)

End point description:

Plasma samples were collected at 5 timepoints on day 3 of daptomycin treatment. The analysis population included all enrolled participants who received at least 3 consecutive IV infusions of study treatment, had at least 1 pharmacokinetic (PK) sample following study drug administration, and did not have any protocol violations affecting the PK profile. The mean of Cmax (µg/mL) is presented in each age category in participants with cSSTI and in the age category 1-<2 years in bacteremia. In the other bacteremia categories, individual Cmax is presented.

End point type	Secondary

End point timeframe:

On Day 3 of study drug administration- pre dose, 15 minutes, 1 hour, 4 hours, and 12 hours after the end of infusion.

End point values	cSSTI	Bacteremia		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	4		
Units: µg/mL				
arithmetic mean (standard deviation)				
Age Category 1-<2 (n=3, 2)	91.7 (± 6.66)	104 (± 8.70)		
Age Category 2-6 (n=3, 0)	80.3 (± 4.48)	0 (± 0)		
Age Category 7-11 (n=5, 1)	64.4 (± 15.1)	73.1 (± 0)		
Age Category 12-17 (n=3, 1)	49.3 (± 1.33)	94.0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Reach Maximum Plasma Concentration (Tmax)

End point title	Median Time to Reach Maximum Plasma Concentration (Tmax)

End point description:

Plasma samples were collected at 5 timepoints on day 3 of daptomycin treatment. The analysis population included all enrolled participants who received at least 3 consecutive IV infusions of study treatment, had at least 1 pharmacokinetic (PK) sample following study drug administration, and did not have any protocol violations affecting the PK profile. The Tmax (hr) is the sampling time at which Cmax occurred and the median Tmax in hours is presented in each age category in participants with cSSTI, and in the age category 1-<2 years in bacteremia. In the other bacteremia age categories, individual Tmax is presented.

End point type	Secondary

End point timeframe:

On Day 3 of study drug administration- pre dose, 15 minutes, 1 hour, 4 hours, and 12 hours after the end of infusion.

End point values	cSSTI	Bacteremia		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	4		
Units: Hours				
median (full range (min-max))				
Age Category 1-<2 (n-3, 2)	1.33 (1.33 to 1.37)	1.27 (1.20 to 1.33)		
Age Category 2-6 (n=3,0)	1.23 (1.12 to 1.27)	0 (0 to 0)		
Age Category 7-11 (n=5,1)	0.833 (0.783 to 1.00)	0.800 (0.800 to 0.800)		
Age Category 12-17 (n=3, 1)	0.750 (0.750 to 0.750)	0.733 (0.733 to 0.733)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Apparent Half-life (t½)

End point title	Mean Apparent Half-life (t½)

End point description:

t½ (hr) was calculated based on the plasma concentration data at 1, 4, and 12 hours after the end of infusion. The analysis population included all enrolled participants who received at least 3 consecutive IV infusions of study treatment, had at least 1 pharmacokinetic (PK) sample following study drug administration, and did not have any protocol violations affecting the PK profile. The mean of t½ is presented in each age category in participants with cSSTI. In participants with bacteremia, the individual t½ presented.

End point type	Secondary

End point timeframe:

On Day 3 of study drug administration - 1 hour, 4 hours, and 12 hours after the end of infusion

End point values	cSSTI	Bacteremia		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	3		
Units: Hours				
arithmetic mean (standard deviation)				
Age Category 1-<2 (n=3, 1)	4.94 (± 0.460)	4.46 (± 0)		
Age Category 2-6 (n=3, 0)	3.87 (± 0.514)	0 (± 0)		
Age Category 7-11 (n=5, 1)	5.07 (± 1.09)	5.85 (± 0)		
Age Category 12-17 (n=3, 1)	5.71 (± 0.942)	3.98 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Total Body Clearance at Steady State (CLss/wt)

End point title	Mean Total Body Clearance at Steady State (CLss/wt)

End point description:

Plasma samples collected at 5 time points on day 3 of daptomycin treatment were used to determine body weight adjusted clearance of daptomycin at steady state (mL/hr/kg). The analysis population included all enrolled participants who received at least 3 consecutive IV infusions of study treatment, had at least 1 pharmacokinetic (PK) sample following study drug administration, and did not have any protocol violations affecting the PK profile. The mean of CLss/wt is presented in each age category in participants with cSSTI. In participants with bacteremia, the individual CLss is presented.

End point type	Secondary

End point timeframe:

On Day 3 of study drug administration- pre dose, 15 minutes, 1 hour, 4 hours, and 12 hours after the end of infusion.

End point values	cSSTI	Bacteremia		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	3		
Units: mL/hr/kg				
arithmetic mean (standard deviation)				
Age Category 1-<2 (n=3, 1)	17.8 (± 2.86)	23.9 (± 0)		
Age Category 2-6 (n=3, 0)	21.1 (± 2.69)	0 (± 0)		
Age Category 7-11 (n=5, 1)	19.4 (± 8.27)	15.0 (± 0)		
Age Category 12-17 (n=3, 1)	15.8 (± 0.917)	16.6 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Volume of Distribution at Steady State (Vss)

End point title	Mean Volume of Distribution at Steady State (Vss)

End point description:

Plasma samples collected at 5 time points on day 3 of daptomycin treatment were used to determine the Vss (mL) of daptomycin for each infection type and age category. The analysis population included all enrolled participants who received at least 3 consecutive IV infusions of study treatment, had at least 1 pharmacokinetic (PK) sample following study drug administration, and did not have any protocol violations affecting the PK profile. The mean Vss is presented in each age category in participants with cSSTI. In participants with bacteremia, the individual Vss is presented.

End point type	Secondary

End point timeframe:

On Day 3 of study drug administration- pre dose, 15 minutes, 1 hour, 4 hours, and 12 hours after the end of infusion.

End point values	cSSTI	Bacteremia		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	3		
Units: mL				
arithmetic mean (standard deviation)				
Age Category 1-<2 (n=3, 1)	1146 (± 299)	1918 (± 0)		
Age Category 2-6 (n=3, 0)	1753 (± 486)	0 (± 0)		
Age Category 7-11 (n=5, 1)	3929 (± 2032)	4013 (± 0)		
Age Category 12-17 (n=3, 1)	6414 (± 1086)	5106 (± 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 56 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0
Reporting groups	
Reporting group title	Daptomycin

Reporting group description: -

Serious adverse events	Daptomycin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Daptomycin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 18 (55.56%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Platelet count increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
General disorders and administration site conditions			
Catheter site related reaction			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Infusion site swelling			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Enterocolitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastrointestinal mucosal disorder			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

Alopecia subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 2 / 18 (11.11%) 2		
Infections and infestations Gastroenteritis viral subjects affected / exposed occurrences (all) Genital candidiasis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was concluded due to the difficulty of enrolling pediatric patients into the study during the COVID-19 pandemic. This study concluded enrollment with 18 participants, versus the 20 that were originally planned.

Notes: