Clinical trial results:
A Phase 2, Randomized, Active Comparator-Controlled, Multicenter, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam (MK-7625A) Versus Meropenem in Pediatric Subjects with Complicated Urinary Tract Infection, Including Pyelonephritis

Summary

EudraCT number	2016-004153-32
Trial protocol	HU PL GR Outside EU/EEA RO
Global end of trial date	20 January 2021

Results information

Result version number	v1 (current)
This version publication date	14 July 2021
First version publication date	14 July 2021

Trial information

Trial identification

Sponsor protocol code	7625A-034

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03230838
WHO universal trial number (UTN)	-

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-001142-PIP01-11
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	03 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2020
Global end of trial reached?	Yes
Global end of trial date	20 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aims to evaluate the safety and tolerability of MK-7625A (ceftolozane/tazobactam) compared with that of meropenem in pediatric participants with complicated urinary tract infection (cUTI), including pyelonephritis.

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	26 April 2018
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	Greece: 36
Country: Number of subjects enrolled	Hungary: 22
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	Ukraine: 22
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	134
EEA total number of subjects	75

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	3
Infants and toddlers (28 days-23	50

months)	
Children (2-11 years)	61
Adolescents (12-17 years)	20
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:

Males and females from birth (>32 weeks gestational age and ≥7 days postnatal) to <18 years of age with complicated urinary tract infection (cUTI), including pyelonephritis, were enrolled in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Ceftolozane/Tazobactam

Arm description:

Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum 1 g and 0.5 g/dose) administered intravenously (IV) every 8 hours for 7-14 days

Arm type	Experimental
Investigational medicinal product name	Ceftolozane/Tazobactam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 to <18 years of age: Ceftolozane 1 g/dose; Tazobactam 0.5 g/dose via a 60-minute (±10 minutes) IV infusion every 8 hours for 7-14 days.
<12 years of age: Ceftolozane 20 mg/kg with Tazobactam 10 mg/kg (not to exceed Ceftolozane 1 g and Tazobactam 0.5 g) via a 60-minute (±10 minutes) IV infusion every 8 hours for 7-14 days.

Arm title	Meropenem

Arm description:

Meropenem 20 mg/kg (maximum 1 g/dose) administered IV every 8 hours for 7-14 days

Arm type	Active comparator
Investigational medicinal product name	Meropenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Meropenem 20 mg/kg to maximum 1 g/ dose every 8 hours for 7-14 days

Number of subjects in period 1	Ceftolozane/Tazobactam	Meropenem
Started	101	33
Treated	100	33
Completed	97	33
Not completed	4	0
Consent withdrawn by subject	3	-
Temperature excursion	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ceftolozane/Tazobactam
Reporting group description:	
Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum 1 g and 0.5 g/dose) administered intravenously (IV) every 8 hours for 7-14 days	
Reporting group title	Meropenem
Reporting group description:	
Meropenem 20 mg/kg (maximum 1 g/dose) administered IV every 8 hours for 7-14 days	

Reporting group values	Ceftolozane/Tazobactam	Meropenem	Total
Number of subjects	101	33	134
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	2	1	3
Infants and toddlers (28 days-23 months)	38	12	50
Children (2-11 years)	46	15	61
Adolescents (12-17 years)	15	5	20
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	5.3	5.5	
standard deviation	± 5.3	± 5.7	-
Gender Categorical Units: Subjects			
Female	65	20	85
Male	36	13	49
Race Units: Subjects			
Asian	1	0	1
White	100	33	133
Ethnicity Units: Subjects			
Hispanic Or Latino	9	5	14
Not Hispanic Or Latino	81	27	108
Not Reported	1	0	1
Unknown	10	1	11

End points

End points reporting groups	
Reporting group title	Ceftolozane/Tazobactam
Reporting group description:	
Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum 1 g and 0.5 g/dose) administered intravenously (IV) every 8 hours for 7-14 days	
Reporting group title	Meropenem
Reporting group description:	
Meropenem 20 mg/kg (maximum 1 g/dose) administered IV every 8 hours for 7-14 days	

Primary: Number of participants with ≥1 adverse events (AEs)	
End point title	Number of participants with ≥1 adverse events (AEs)
End point description:	
An adverse event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), 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 (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an AE. The population analyzed was all randomized participants who received any amount of study treatment.	
End point type	Primary
End point timeframe:	
Up to Day 88	

End point values	Ceftolozane/Tazobactam	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	33		
Units: Participants	59	20		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T minus Mero)
Statistical analysis description:	
The Miettinen & Nurminen method was used.	
Comparison groups	Ceftolozane/Tazobactam v Meropenem
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.7
upper limit	17.9

Primary: Number of participants discontinuing study therapy due to an AE

End point title	Number of participants discontinuing study therapy due to an AE

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), 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 (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an AE. The population analyzed was all randomized participants who received any amount of study treatment.

End point type	Primary

End point timeframe:

Up to Day 15

End point values	Ceftolozane/Tazobactam	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	33		
Units: Participants	1	0		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T minus Mero)

Statistical analysis description:

The Miettinen & Nurminen method was used.

Comparison groups	Ceftolozane/Tazobactam v Meropenem
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.5
upper limit	5.5

Secondary: Percentage of participants with a clinical response of cure at the Test of Cure Visit

End point title	Percentage of participants with a clinical response of cure at the Test of Cure Visit

End point description:

Clinical response of cure is complete resolution or marked improvement in signs and symptoms of the complicated urinary tract infection (cUTI) or return to pre-infection signs and symptoms, such that no further antibiotic therapy (IV or oral) is required for the treatment of the cUTI. The 95% CIs of each treatment are unstratified Wilson CIs. The population analyzed was all randomized participants who received any amount of study treatment and have at least 1 acceptable causative uropathogen identified from a study-qualifying baseline urine culture.

End point type	Secondary

End point timeframe:

Up to Test of Cure Visit (up to 35 days)

End point values	Ceftolozane/Tazobactam	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	24		
Units: Percentage of participants				
number (confidence interval 95%)	88.7 (79.31 to 94.18)	95.8 (79.76 to 99.26)		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T minus Mero)

Statistical analysis description:

The Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights was used. If there was a zero count in any class of the stratum, the groups with the lower count were pooled with its near age group stratum in the model.

Comparison groups	Ceftolozane/Tazobactam v Meropenem
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.99
upper limit	10.05

Secondary: Percentage of participants with a clinical response of cure at the End of

Treatment Visit

End point title	Percentage of participants with a clinical response of cure at the End of Treatment Visit

End point description:

Clinical response of cure is complete resolution or marked improvement in signs and symptoms of the cUTI or return to pre-infection signs and symptoms, such that no further antibiotic therapy (IV or oral) is required for the treatment of the cUTI. The 95% CIs of each treatment are unstratified Wilson CIs. The population analyzed was all randomized participants who received any amount of study treatment and have at least 1 acceptable causative uropathogen identified from a study-qualifying baseline urine culture.

End point type	Secondary

End point timeframe:

Up to 48 hours after last oral dose (Up to 19 days)

End point values	Ceftolozane/Tazobactam	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	24		
Units: Percentage of participants				
number (confidence interval 95%)	94.4 (86.39 to 97.79)	100.0 (86.20 to 100.00)		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T minus Mero)

Statistical analysis description:

The Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights was used. If there was a zero count in any class of the stratum, the groups with the lower count were pooled with its near age group stratum in the model.

Comparison groups	Ceftolozane/Tazobactam v Meropenem
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.09
upper limit	8.88

Secondary: Percentage of participants with microbiological eradication of all baseline pathogens at the Test of Cure Visit

End point title	Percentage of participants with microbiological eradication of all baseline pathogens at the Test of Cure Visit

End point description:

Microbiological eradication of all baseline pathogens is defined as a postbaseline urine culture shows all

uropathogens found at baseline at ≥10^5 colony-forming units (CFU)/mL are reduced to <10^4 CFU/mL. The 95% CIs of each treatment are unstratified Wilson CIs. The population analyzed was all randomized participants who received any amount of study treatment and have at least 1 acceptable causative uropathogen identified from a study-qualifying baseline urine culture.

End point type	Secondary

End point timeframe:

Up to Test of Cure Visit (up to 35 days)

End point values	Ceftolozane/Tazobactam	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	24		
Units: Percentage of participants				
number (confidence interval 95%)	84.5 (74.35 to 91.12)	87.5 (69.00 to 95.66)		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T minus Mero)

Statistical analysis description:

The Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights was used. If there was a zero count in any class of the stratum, the groups with the lower count were pooled with its near age group stratum in the model.

Comparison groups	Ceftolozane/Tazobactam v Meropenem
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.13
upper limit	17.4

Secondary: Percentage of participants with microbiological eradication of all baseline pathogens at the End of Treatment Visit

End point title	Percentage of participants with microbiological eradication of all baseline pathogens at the End of Treatment Visit

End point description:

Microbiological eradication of all baseline pathogens is defined as a postbaseline urine culture shows all uropathogens found at baseline at ≥10^5 CFU/mL are reduced to <10^4 CFU/mL. The 95% CIs of each treatment are unstratified Wilson CIs.The population analyzed was all randomized participants who received any amount of study treatment and have at least 1 acceptable causative uropathogen identified from a study-qualifying baseline urine culture.

End point type	Secondary

End point timeframe:

Up to 48 hours after last oral dose (Up to 19 days)

End point values	Ceftolozane/Tazobactam	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	24		
Units: Percentage of participants				
number (confidence interval 95%)	93.0 (84.55 to 96.95)	95.8 (79.76 to 99.26)		

Statistical analyses

Statistical analysis title	Difference in Percentage (C/T minus Mero)

Statistical analysis description:

The Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights was used. If there was a zero count in any class of the stratum, the groups with the lower count were pooled with its near age group stratum in the model.

Comparison groups	Ceftolozane/Tazobactam v Meropenem
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.67
upper limit	13.41

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs): From treatment (Day 1) up to 88 days. All-cause mortality: From randomization (Day 1) up to 88 days.

Adverse event reporting additional description:

For all-cause mortality the population analyzed was all randomized participants. For AEs the population analyzed was all randomized participants who received any amount of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Meropenem

Reporting group description:

Meropenem 20 mg/kg (maximum 1 g/dose) administered IV every 8 hours for 7-14 days

Reporting group title	Ceftolozane/Tazobactam

Reporting group description:

Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum 1 g and 0.5 g/dose) administered intravenously (IV) every 8 hours for 7-14 days

Serious adverse events	Meropenem	Ceftolozane/Tazobactam	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 33 (6.06%)	3 / 100 (3.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 33 (3.03%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			

subjects affected / exposed	0 / 33 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 33 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 100 (1.00%)	
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	Meropenem	Ceftolozane/Tazobactam	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 33 (30.30%)	25 / 100 (25.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 33 (6.06%)	4 / 100 (4.00%)	
occurrences (all)	2	4	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 33 (6.06%)	4 / 100 (4.00%)	
occurrences (all)	2	4	
Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	3 / 33 (9.09%)	7 / 100 (7.00%)	
occurrences (all)	3	7	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 33 (0.00%)	6 / 100 (6.00%)	
occurrences (all)	0	9	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	3 / 33 (9.09%)	7 / 100 (7.00%)	
occurrences (all)	3	7	
Infections and infestations			
Rhinitis			
subjects affected / exposed	2 / 33 (6.06%)	2 / 100 (2.00%)	
occurrences (all)	2	2	
Urinary tract infection			
subjects affected / exposed	3 / 33 (9.09%)	1 / 100 (1.00%)	
occurrences (all)	3	1	
Vulvovaginitis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 100 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2019	Amendment 2 combined enrollment targets for groups 3-5 with a companion study of ceftolozane/tazobactam in pediatric complicated urinary tract infections. This allowed greater flexibility in enrollment targets for Groups 3-5 (the youngest cohort of children) and facilitated enrollment of a sufficient number of participants to evaluate safety and pharmacokinetics in both study populations and enabled timely completion of the studies.
08 October 2020	Amendment 3 removed the minimum number of at least 4 participants per study required to be enrolled in Groups 3, 4, and 5 and reduced minimum enrollment targets for Groups 3 and 5. Individual study age group minimum requirements for Groups 3-5 were removed to facilitate more timely availability of important pediatric data to health care providers and participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported