Clinical trial results:
Randomized, Double-Blind, Multi-Center Study of Cefepime/AAI101 in Hospitalized Adults With Complicated Urinary Tract Infections, Including Acute Pyelonephritis

Summary

EudraCT number	2016-005161-31
Trial protocol	HU PL
Global end of trial date	14 February 2018

Results information

Result version number	v1 (current)
This version publication date	21 May 2021
First version publication date	21 May 2021

Trial information

Trial identification

Sponsor protocol code	AT-201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Allecra Therapeutics SAS
Sponsor organisation address	10, rue Alexandre Freund, Saint-Louis, France, 68300
Public contact	Head of Regulatory Affairs, Allecra Therapeutics SAS, +33 389689876, oml@allecra.com
Scientific contact	Head of Regulatory Affairs, Allecra Therapeutics SAS, +33 389689876, oml@allecra.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2018
Global end of trial reached?	Yes
Global end of trial date	14 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the optimal cefepime/AAI101 combination dose to be used in future Phase 3 studies via PK/PD modelling to assess the Probability of Target Attainment (PTA) and the effect of treatment on liver enzymes.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	05 September 2017
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	Ukraine: 20
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Hungary: 6
Worldwide total number of subjects	45
EEA total number of subjects	25

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)	0
Adults (18-64 years)	30
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Hospitalized adults with complicated urinary tract infection (cUTI), including acute pyelonephritis were recruited between 05 September 2017 and 14 February 2018 in 17 sites in 4 countries.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects were not to be randomised to trial treatment if any one of the trial specific entry criteria were violated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 - Cefepime 1g / Enmetazobactam 500mg

Arm description:

In cohort 1, subjects were randomly assigned in a 2:1 ratio to receive cefepime 1 g/AAI101 500 mg q8h or cefepime 1 g q8h.

Arm type	Experimental
Investigational medicinal product name	Cefepime 1g
Investigational medicinal product code	FEP
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were treated with cefepime 1 g/enmetazobactam 500 mg i.v. infusion over 2 hours q8h

Investigational medicinal product name	Enmetazobactam (formerly AAI101) 500mg
Investigational medicinal product code	EMT
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were treated with cefepime 1 g/enmetazobactam 500 mg i.v. infusion over 2 hours q8h

Arm title	Cohort 1 - Cefepime 1g

Arm description:

In cohort 1, subjects were randomly assigned in a 2:1 ratio to receive cefepime 1 g/AAI101 500 mg q8h or cefepime 1 g q8h.

Arm type	Active comparator
Investigational medicinal product name	Cefepime 1g
Investigational medicinal product code	FEP
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients were treated with cefepime 1 g i.v. infusion over 2 hours q8h

Arm title	Cohort 2 - Cefepime 2g / Enmetazobactam 750mg

Arm description:

In cohort 2, subjects were randomly assigned in a 2:1 ratio to receive cefepime 2 g/AAI101 750 mg q8h or cefepime 2 g q8h.

Arm type	Experimental
Investigational medicinal product name	Cefepime 2g
Investigational medicinal product code	FEP
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were treated with cefepime 2 g/enmetazobactam 750 mg i.v. infusion over 2 hours q8h

Investigational medicinal product name	Enmetazobactam (formerly AAI101) 750mg
Investigational medicinal product code	EMT
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were treated with cefepime 2 g/enmetazobactam 750 mg i.v. infusion over 2 hours q8h

Arm title	Cohort 2 - Cefepime 2g

Arm description:

In cohort 2, subjects were randomly assigned in a 2:1 ratio to receive cefepime 2 g/AAI101 750 mg q8h or cefepime 2 g q8h.

Arm type	Active comparator
Investigational medicinal product name	Cefepime 2g
Investigational medicinal product code	FEP
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were treated with cefepime 2 g i.v. infusion over 2 hours q8h

Number of subjects in period 1	Cohort 1 - Cefepime 1g / Enmetazobactam 500mg	Cohort 1 - Cefepime 1g	Cohort 2 - Cefepime 2g / Enmetazobactam 750mg
Started	15	7	15
Completed	15	7	14
Not completed	0	0	1
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	1

Number of subjects in period 1	Cohort 2 - Cefepime 2g
Started	8
Completed	7
Not completed	1
Consent withdrawn by subject	1
Adverse event, non-fatal	-

Period 2	
Period 2 title	Population PK model
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	No
Arm title	Cefepime/Enmetazobactam MIC = 4 µg/mL
Arm description: -	
Arm type	MIC group
Investigational medicinal product name	Cefepime 2g q8h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 2 g intravenous (i.v.) infusion over 2 hours once every 8 hours (q8h)	
Investigational medicinal product name	Enmetazobactam (formerly AAI101) 500mg q8h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 500 mg intravenous (i.v.) infusion over 2 hours once every 8 hours (q8h)	
Investigational medicinal product name	Cefepime 2g q12h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 2 g intravenous (i.v.) infusion over 2 hours once every 12 hours (q12h)	
Investigational medicinal product name	Enmetazobactam (formerly AAI101) 500mg q12h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 500 mg intravenous (i.v.) infusion over 2 hours once every 12 hours (q12h)	
Arm title	Cefepime/Enmetazobactam MIC = 8 µg/mL

Arm description: -	
Arm type	MIC group
Investigational medicinal product name	Cefepime 2g q8h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 2g intravenous (i.v.) infusion over 2 hours once every 8 hours (q8h)	
Investigational medicinal product name	Enmetazobactam (formerly AAI101) 500mg q8h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 500 mg intravenous (i.v.) infusion over 2 hours once every 8 hours (q8h)	
Investigational medicinal product name	Cefepime 2g q12h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 2 g intravenous (i.v.) infusion over 2 hours once every 12 hours (q12h)	
Investigational medicinal product name	Enmetazobactam (formerly AAI101) 500mg q12h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 500 mg intravenous (i.v.) infusion over 2 hours once every 12 hours (q12h)	
Arm title	Cefepime/Enmetazobactam MIC = 16 µg/mL
Arm description: -	
Arm type	MIC group
Investigational medicinal product name	Cefepime 2g q8h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 2 g intravenous (i.v.) infusion over 2 hours once every 8 hours (q8h)	
Investigational medicinal product name	Enmetazobactam (formerly AAI101) 500mg q8h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 500 mg intravenous (i.v.) infusion over 2 hours once every 8 hours (q8h)	
Investigational medicinal product name	Cefepime 2g q12h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use
Dosage and administration details: 2 g intravenous (i.v.) infusion over 2 hours once every 12 hours (q12h)	
Investigational medicinal product name	Enmetazobactam (formerly AAI101) 500mg q12h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 500 mg intravenous (i.v.) infusion over 2 hours once every 12 hours (q12h)	
Arm title	Cefepime/Enmetazobactam MIC = 32 µg/mL
Arm description: -	
Arm type	MIC group
Investigational medicinal product name	Cefepime 2g q8h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 2 g intravenous (i.v.) infusion over 2 hours once every 8 hours (q8h)	
Investigational medicinal product name	Enmetazobactam (formerly AAI101) 500mg q8h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 500 mg intravenous (i.v.) infusion over 2 hours once every 8 hours (q8h)	
Investigational medicinal product name	Cefepime 2g q12h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 2 g intravenous (i.v.) infusion over 2 hours once every 12 hours (q12h)	
Investigational medicinal product name	Enmetazobactam (formerly AAI101) 500mg q12h
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 500 mg intravenous (i.v.) infusion over 2 hours once every 12 hours (q12h)	

Number of subjects in period 2	Cefepime/Enmetazobactam MIC = 4 µg/mL	Cefepime/Enmetazobactam MIC = 8 µg/mL	Cefepime/Enmetazobactam MIC = 16 µg/mL
Started	1	1	1
Completed	1	1	1

Number of subjects in period 2	Cefepime/Enmetazobactam MIC = 32 µg/mL
Started	1
Completed	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 - Cefepime 1g / Enmetazobactam 500mg
Reporting group description:	
In cohort 1, subjects were randomly assigned in a 2:1 ratio to receive cefepime 1 g/AAI101 500 mg q8h or cefepime 1 g q8h.	
Reporting group title	Cohort 1 - Cefepime 1g
Reporting group description:	
In cohort 1, subjects were randomly assigned in a 2:1 ratio to receive cefepime 1 g/AAI101 500 mg q8h or cefepime 1 g q8h.	
Reporting group title	Cohort 2 - Cefepime 2g / Enmetazobactam 750mg
Reporting group description:	
In cohort 2, subjects were randomly assigned in a 2:1 ratio to receive cefepime 2 g/AAI101 750 mg q8h or cefepime 2 g q8h.	
Reporting group title	Cohort 2 - Cefepime 2g
Reporting group description:	
In cohort 2, subjects were randomly assigned in a 2:1 ratio to receive cefepime 2 g/AAI101 750 mg q8h or cefepime 2 g q8h.	

Reporting group values	Cohort 1 - Cefepime 1g / Enmetazobactam 500mg	Cohort 1 - Cefepime 1g	Cohort 2 - Cefepime 2g / Enmetazobactam 750mg
Number of subjects	15	7	15
Age categorical			
Units: Subjects			
Adults (18-64 years)	9	4	10
From 65 to 74 years	4	2	4
75 years and older	2	1	1
Age continuous			
Units: years			
arithmetic mean	56.7	57.0	49.8
standard deviation	± 18.32	± 18.09	± 19.96
Gender categorical			
Units: Subjects			
Female	11	2	11
Male	4	5	4
Weight			
Units: kg			
arithmetic mean	92.3	80.7	73.1
standard deviation	± 17.03	± 15.20	± 15.82
Height			
Units: cm			
arithmetic mean	168.2	173.3	166.2
standard deviation	± 7.33	± 7.87	± 7.17
Body mass index			
Units: kg/m2			
arithmetic mean	32.5	26.8	26.4
standard deviation	± 5.02	± 4.37	± 5.28
Creatinine clearance			

Units: mL/min			
arithmetic mean	102.8	83.7	110.6
standard deviation	± 35.38	± 28.80	± 43.68

Reporting group values	Cohort 2 - Cefepime 2g	Total	
Number of subjects	8	45	
Age categorical			
Units: Subjects			
Adults (18-64 years)	7	30	
From 65 to 74 years	1	11	
75 years and older	0	4	
Age continuous			
Units: years			
arithmetic mean	37.9		
standard deviation	± 21.09	-	
Gender categorical			
Units: Subjects			
Female	5	29	
Male	3	16	
Weight			
Units: kg			
arithmetic mean	71.0		
standard deviation	± 21.78	-	
Height			
Units: cm			
arithmetic mean	168.5		
standard deviation	± 7.09	-	
Body mass index			
Units: kg/m2			
arithmetic mean	24.7		
standard deviation	± 5.77	-	
Creatinine clearance			
Units: mL/min			
arithmetic mean	95.0		
standard deviation	± 20.55	-	

Subject analysis sets

Subject analysis set title	Modified Intent-to-Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population, defined as all patients who were randomized, included 45 (100.0%) patients. The MITT Population, defined as all patients who met ITT criteria and received any amount of study drug, included 45 (100.0%) patients.

Subject analysis set title	Microbiological Modified Intent-to-Treat Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Microbiological MITT (micro-MITT) Population included all randomized patients who met MITT criteria who had a study qualifying (105 CFU/mL) baseline bacterial pathogen on urine culture or the same pathogen present in concurrent blood and urine cultures that caused cUTI. The micro-MITT Population was the primary efficacy population.

Subject analysis set title	Population PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The population PK models for cefepime and enmetazobactam were applied to conduct a PK/PD target attainment assessment using Monte-Carlo simulations to support the dose selection for both compounds. For cefepime, 4000 patients were simulated, and probabilities of target attainment (PTAs) were calculated for a cefepime dose of 2 g q8h infused i.v. over 2 hours in patients with normal renal function or with mild renal impairment. PTAs were also calculated for patients with moderate renal impairment receiving an adjusted cefepime dose of 2 g once every 12 hours (q12h). For enmetazobactam, 4000 patients were simulated, and PTAs were calculated for ascending doses starting at 100 mg q8h infused i.v. over 2 hours for patients with normal renal function or with mild renal impairment. PTAs were also reported for patients with moderate renal impairment receiving an adjusted enmetazobactam dose administered q12h.

Reporting group values	Modified Intent-to-Treat Population	Microbiological Modified Intent-to-Treat Population	Population PK
Number of subjects	45	39	4
Age categorical Units: Subjects			
Adults (18-64 years)	30	26	
From 65 to 74 years	11	9	
75 years and older	4	4	
Age continuous Units: years			
arithmetic mean	51.1	50.0	
standard deviation	± 19.94	± 20.79	±
Gender categorical Units: Subjects			
Female	29	26	
Male	16	13	
Weight Units: kg			
arithmetic mean	80.1	79.3	
standard deviation	± 19.01	± 19.91	±
Height Units: cm			
arithmetic mean	168.4	168.4	
standard deviation	± 7.44	± 7.32	±
Body mass index Units: kg/m2			
arithmetic mean	28.2	27.8	
standard deviation	± 5.90	± 6.18	±
Creatinine clearance Units: mL/min			
arithmetic mean	101.0	100.5	
standard deviation	± 35.67	± 37.59	±

End points

End points reporting groups

Reporting group title	Cohort 1 - Cefepime 1g / Enmetazobactam 500mg
Reporting group description:	
In cohort 1, subjects were randomly assigned in a 2:1 ratio to receive cefepime 1 g/AAI101 500 mg q8h or cefepime 1 g q8h.	
Reporting group title	Cohort 1 - Cefepime 1g
Reporting group description:	
In cohort 1, subjects were randomly assigned in a 2:1 ratio to receive cefepime 1 g/AAI101 500 mg q8h or cefepime 1 g q8h.	
Reporting group title	Cohort 2 - Cefepime 2g / Enmetazobactam 750mg
Reporting group description:	
In cohort 2, subjects were randomly assigned in a 2:1 ratio to receive cefepime 2 g/AAI101 750 mg q8h or cefepime 2 g q8h.	
Reporting group title	Cohort 2 - Cefepime 2g
Reporting group description:	
In cohort 2, subjects were randomly assigned in a 2:1 ratio to receive cefepime 2 g/AAI101 750 mg q8h or cefepime 2 g q8h.	
Reporting group title	Cefepime/Enmetazobactam MIC = 4 µg/mL
Reporting group description: -	
Reporting group title	Cefepime/Enmetazobactam MIC = 8 µg/mL
Reporting group description: -	
Reporting group title	Cefepime/Enmetazobactam MIC = 16 µg/mL
Reporting group description: -	
Reporting group title	Cefepime/Enmetazobactam MIC = 32 µg/mL
Reporting group description: -	
Subject analysis set title	Modified Intent-to-Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT Population, defined as all patients who were randomized, included 45 (100.0%) patients. The MITT Population, defined as all patients who met ITT criteria and received any amount of study drug, included 45 (100.0%) patients.	
Subject analysis set title	Microbiological Modified Intent-to-Treat Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The Microbiological MITT (micro-MITT) Population included all randomized patients who met MITT criteria who had a study qualifying (105 CFU/mL) baseline bacterial pathogen on urine culture or the same pathogen present in concurrent blood and urine cultures that caused cUTI. The micro-MITT Population was the primary efficacy population.	
Subject analysis set title	Population PK
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The population PK models for cefepime and enmetazobactam were applied to conduct a PK/PD target attainment assessment using Monte-Carlo simulations to support the dose selection for both compounds. For cefepime, 4000 patients were simulated, and probabilities of target attainment (PTAs) were calculated for a cefepime dose of 2 g q8h infused i.v. over 2 hours in patients with normal renal function or with mild renal impairment. PTAs were also calculated for patients with moderate renal impairment receiving an adjusted cefepime dose of 2 g once every 12 hours (q12h). For enmetazobactam, 4000 patients were simulated, and PTAs were calculated for ascending doses starting at 100 mg q8h infused i.v. over 2 hours for patients with normal renal function or with mild renal impairment. PTAs were also reported for patients with moderate renal impairment receiving an adjusted enmetazobactam dose administered q12h.	

Primary: Percentage of Simulated Patients With Complicated Urinary Tract Infection Achieving Pharmacokinetic/Pharmacodynamic Targets for Cefepime and AAI101 by Renal Function

End point title	Percentage of Simulated Patients With Complicated Urinary Tract Infection Achieving Pharmacokinetic/Pharmacodynamic Targets for Cefepime and AAI101 by Renal Function

End point description:

This table shows PTAs for enmetazobactam 500 mg applying a PK/PD target of 46% fT >CT (CT = 2 µg/mL) and PTAs for cefepime 2 g applying a PK/PD target of 68% fT >MIC (MIC = 4, 8, 16, and 32 µg/mL) in simulated patients with cUTI by renal function. For the enmetazobactam PK/PD target of 46% fT >CT (CT = 2 µg/mL), the PTAs were >98% for all renal function patient groups. For the cefepime PK/PD target of 68% fT >MIC, the PTAs were >95% for all renal function patient groups for cefepime/enmetazobactam MICs of 4 and 8 µg/mL. For a cefepime/enmetazobactam MIC >=16 µg/mL, the PTAs for cefepime were <95%.
Normal renal function was defined as creatinine clearance >90 mL/min. Mild renal impairment was defined as creatinine clearance 60 to <90 mL/min. Moderate renal impairment was defined as creatinine clearance 30 to <60 mL/min.
i.v. = intravenous(ly); MIC = minimum inhibitory concentration; PD = pharmacodynamic; PK = pharmacokinetic; q8h = once every 8 hours; q12h = once every 12 hours.

End point type	Primary

End point timeframe:

End of Treatment

End point values	Cefepime/Enmetazobactam MIC = 4 µg/mL	Cefepime/Enmetazobactam MIC = 8 µg/mL	Cefepime/Enmetazobactam MIC = 16 µg/mL	Cefepime/Enmetazobactam MIC = 32 µg/mL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	1	1
Units: Percentage				
number (not applicable)				
Renal function normal / Cefepime 2g q8h	99.8	95.6	57.6	1.3
Renal function normal / Enmetazobactam 500mg q8h	98.4	98.4	98.4	98.4
Mild renal impairment / Cefepime 2g q8h	100	99.9	94.8	20.4
Mild renal impairment / Enmetazobactam 500mg q8h	99.2	99.2	99.2	99.2
Moderate renal impairment / Cefepime 2g q12h	100	99.5	83.5	3.4
Moderate renal impairmt / Enmetazobact 500mg q12h	98.1	98.1	98.1	98.1

Statistical analyses

Statistical analysis title	PK modeling and simulation for PTA

Statistical analysis description:

Monte-Carlo simulations were performed, using a cUTI population that was similar in the covariates to the study population. The aim was to calculate Probabilities of target attainment (PTAs) for a dose of 2g cefepime and 500 mg enmetazobactam, respectively, given q8h as 2h infusion and adjusted to q12h for patients with moderate renal impairment. 4000 patients were simulated for each dosing group. To comply with data entry restrictions, patient number in each comparison group is set to 1.

Comparison groups	Cefepime/Enmetazobactam MIC = 4 µg/mL v

	Cefepime/Enmetazobactam MIC = 8 µg/mL v Cefepime/Enmetazobactam MIC = 16 µg/mL v Cefepime/Enmetazobactam MIC = 32 µg/mL
Number of subjects included in analysis	4
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 1 [2]
Method	Computed modeling
Parameter estimate	descriptive

Notes:

[1] - Monte Carlo simulation.

[2] - Not applicable

Other pre-specified: Microbiological Response Based on EMA Colony Forming Units/mL Criteria

End point title	Microbiological Response Based on EMA Colony Forming Units/mL Criteria

End point description:

This table summarizes the per-patient microbiological response based on EMA criteria for the micro-MITT Population.
Assessment of Microbiological Outcome
- Microbiological eradication – baseline qualifying bacterial pathogen was reduced to <10^3 CFU/mL according to the European Medicines Agency (EMA) criteria;
- Microbiological persistence – urine culture grew >=10^3 CFU/mL (EMA criteria) of the baseline qualifying pathogen identified at study entry; and
- Microbiological indeterminate – no urine culture was available, or the culture could not be interpreted for any reason.

Percentage was calculated using the number of patients in the column heading as the denominator.
CFU = colony forming units; FDA = Food and Drug Administration.

End point type	Other pre-specified

End point timeframe:

Time Points for Microbiological Response

End point values	Cohort 1 - Cefepime 1g / Enmetazobactam 500mg	Cohort 1 - Cefepime 1g	Cohort 2 - Cefepime 2g / Enmetazobactam 750mg	Cohort 2 - Cefepime 2g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	7	11	8
Units: Number of Subjects				
Day 3 - Eradication	12	7	10	7
Day 3 - Persistance	1	0	0	0
Day 3 - Indeterminate	0	0	1	1
End of Treatment - Eradication	11	5	10	7
End of Treatment - Persistance	1	1	0	0
End of Treatment - Indeterminate	1	1	1	1
Test of Cure - Eradication	10	7	10	4
Test of Cure - Persistence	3	0	0	3
Test of Cure - Indeterminate	0	0	1	1
Late Follow-up - Eradication	6	6	9	4
Late Follow-up - Persistence	5	1	1	3
Late Follow-up - Indeterminate	2	0	1	1

Statistical analyses

No statistical analyses for this end point

Post-hoc: Microbiological Response Based on EMA Colony Forming Units/mL Criteria – Patients With Positive Response of Extended-Spectrum β-Lactamase Ceftazidime and/or Cefotaxime Tests at Baseline

End point title	Microbiological Response Based on EMA Colony Forming Units/mL Criteria – Patients With Positive Response of Extended-Spectrum β-Lactamase Ceftazidime and/or Cefotaxime Tests at Baseline

End point description:

This table summarizes the ad-hoc analysis of the per-patient microbiological response based on EMA criteria in patients with an ESBL-producing organism (i.e. positive response to ESBL ceftazidime and/or cefotaxime tests at baseline) for the micro-MITT Population.
Assessment of Microbiological Outcome.

- Microbiological eradication – baseline qualifying bacterial pathogen was reduced to <10^3 CFU/mL according to the European Medicines Agency (EMA) criteria;
- Microbiological persistence – urine culture grew >=10^3 CFU/mL (EMA criteria) of the baseline qualifying pathogen identified at study entry; and
- Microbiological indeterminate – no urine culture was available, or the culture could not be interpreted for any reason.

Percentage was calculated using the number of patients in the column heading as the denominator.
CFU = colony forming units; EMA = European Medicines Agency.

End point type	Post-hoc

End point timeframe:

Time points for microbiological response

End point values	Cohort 1 - Cefepime 1g / Enmetazobactam 500mg	Cohort 1 - Cefepime 1g	Cohort 2 - Cefepime 2g / Enmetazobactam 750mg	Cohort 2 - Cefepime 2g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	1
Units: Number of Subjects				
Day 3 - Eradication	3	3	4	1
Day 3 - Persistence	0	0	0	0
Day 3 - Indeterminate	0	0	0	0
End of Treatment - Eradication	3	1	4	1
End of Treatment - Persistence	0	1	0	0
End of Treatment - Indeterminate	0	1	0	0
Test of Cure - Eradication	2	3	4	0
Test of Cure - Persistence	1	0	0	1
Test of Cure - Indeterminate	0	0	0	0
Late Follow-up - Eradication	1	3	3	0
Late Follow-up - Persistence	2	0	1	1
Late Follow-up - Indeterminate	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

15-Sep-2017 to 14-Feb-2018

Adverse event reporting additional description:

This overview provides information on all adverse events (AEs) for the Safety Population, which included all patients who received at least 1 dose of study drug during the study.
Percentage was calculated using the number of patients in the column heading as the denominator. Only AEs up to 28 days post randomization were considered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Safety Population

Reporting group description:

The Safety Population included all patients who received at least 1 dose of study drug during the study.

Reporting group title	Cohort 1 - Cefepime 1 g/ Enmetazobactam 500 mg

Reporting group description: -

Reporting group title	Cohort 1 - Cefepime 1 g

Reporting group description: -

Reporting group title	Cohort 2 - Cefepime 2 g/ Enmetazobactam 750 mg

Reporting group description: -

Reporting group title	Cohort 2 - Cefepime 2 g

Reporting group description: -

Serious adverse events	Safety Population	Cohort 1 - Cefepime 1 g/ Enmetazobactam 500 mg	Cohort 1 - Cefepime 1 g
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 45 (4.44%)	0 / 15 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal cancer metastatic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 45 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2 - Cefepime 2 g/ Enmetazobactam 750 mg	Cohort 2 - Cefepime 2 g	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal cancer metastatic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Safety Population	Cohort 1 - Cefepime 1 g/ Enmetazobactam 500 mg	Cohort 1 - Cefepime 1 g
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 45 (42.22%)	9 / 15 (60.00%)	3 / 7 (42.86%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Phlebitis superficial			
subjects affected / exposed	1 / 45 (2.22%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			

Edema peripheral			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Nervousness			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Investigations			
ALT increased			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
AST increased			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
ECG-QT prolonged			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Dilatation atrial			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Left ventricular hypertrophy			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			

Headache			
subjects affected / exposed	4 / 45 (8.89%)	3 / 15 (20.00%)	0 / 7 (0.00%)
occurrences (all)	4	3	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	1 / 45 (2.22%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	2 / 45 (4.44%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 45 (2.22%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	2 / 45 (4.44%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Endocrine disorders			
Hypoaldosteronism			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Hordeolum			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Respiratory tract infection			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection fungal			

subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Glucose tolerance impaired			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Hypomagnesaemia			
subjects affected / exposed	1 / 45 (2.22%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Impaired fasting glucose			
subjects affected / exposed	1 / 45 (2.22%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 45 (2.22%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1

Non-serious adverse events	Cohort 2 - Cefepime 2 g/ Enmetazobactam 750 mg	Cohort 2 - Cefepime 2 g	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 15 (26.67%)	3 / 8 (37.50%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Phlebitis superficial			
subjects affected / exposed	0 / 15 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Edema peripheral			

subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Nervousness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Investigations			
ALT increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
AST increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
ECG-QT prolonged			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Dilatation atrial			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Left ventricular hypertrophy			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 15 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	2 / 15 (13.33%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypoaldosteronism			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Hordeolum			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection fungal			

subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Glucose tolerance impaired			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Impaired fasting glucose			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	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

None reported