

**Clinical trial results:****A Phase 3, Randomized, Double-Blind, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Cefepime- AAI101 Compared to Piperacillin/Tazobactam in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, in Adults****Summary**

EudraCT number	2017-004868-35
Trial protocol	LT LV ES BG SK PL HU HR
Global end of trial date	26 November 2019

Results information

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

Trial information**Trial identification**

Sponsor protocol code	AT-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03687255
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 122269

Notes:

Sponsors

Sponsor organisation name	Allegra Therapeutics SAS
Sponsor organisation address	10, rue Alexandre Freund, Saint-Louis, France, 68300
Public contact	Head of Regulatory Affairs, Allegra Therapeutics SAS, +33 389689876 , oml@allecra.com
Scientific contact	Head of Regulatory Affairs, Allegra 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	30 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2019
Global end of trial reached?	Yes
Global end of trial date	26 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the efficacy of cefepime-AAI101 compared to Piperacillin/Tazobactam in the treatment of cUTI, including acute pyelonephritis (AP).

Protection of trial subjects:

Patients were monitored for safety throughout the duration of the study. Safety assessments included vital signs, physical examinations, laboratory assessments, adverse event (AE) assessments, and electrocardiograms (ECGs). A triplicate 12-lead ECG was performed at Screening and Day 4. A pregnancy test was performed at Screening and TOC for female patients of childbearing potential. A Data Safety and Monitoring Board (DSMB) was established with the aim to safeguard the interests of the study participants, Investigators, and the Sponsor; to assess the safety of the study's interventions; to monitor the overall conduct of the study; and to protect its integrity and validity. The DSMB worked under an approved DSMB Charter.

Background therapy: -

Evidence for comparator:

Piperacillin/tazobactam has been the mainstay of empiric treatment of serious hospital infections; however, in many regions its efficacy has eroded due to local emergence or spread of new, more aggressive ESBLs and carbapenemases.

Actual start date of recruitment	28 September 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	Argentina: 4
Country: Number of subjects enrolled	Belarus: 70
Country: Number of subjects enrolled	Georgia: 66
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Slovakia: 24
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Croatia: 41
Country: Number of subjects enrolled	Bulgaria: 103
Country: Number of subjects enrolled	Estonia: 50
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Latvia: 36
Country: Number of subjects enrolled	Lithuania: 67
Country: Number of subjects enrolled	Mexico: 49
Country: Number of subjects enrolled	Peru: 20

Country: Number of subjects enrolled	Russian Federation: 164
Country: Number of subjects enrolled	Serbia: 27
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Ukraine: 240
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	1041
EEA total number of subjects	399

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)	639
From 65 to 84 years	380
85 years and over	22

Subject disposition

Recruitment

Recruitment details:

Study Sites: 90 sites in Argentina, Belarus, Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Lithuania, Mexico, Peru, Poland, Russia, Serbia, Slovakia, South Africa, Spain, Ukraine, and the United States

Study Period: Approximately 61 weeks

Initiation Date: 24 September 2018

Completion Date: 26 November 2019

Pre-assignment

Screening details:

Adult patients ≥ 18 years of age with a clinical diagnosis of cUTI or AP requiring hospitalisation and at least 7 days of IV treatment were screened. Patients who received potentially effective systemic antibacterial therapy for a continuous duration of >24 hours during the previous 72 hours before the study-qualifying baseline urine were excluded.

Period 1

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

Blinding implementation details:

Randomization was coordinated through a centralized Interactive Response Technology system. To ensure balance among the treatment groups, randomization was stratified by: Type of infection, prior antibiotic therapy, and geographic region.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cefepime-Enmetazobactam

Arm description:

2 g cefepime (FEP) plus 500 mg enmetazobactam (EMT) infused over a period of 2 hours once every 8 hours (q8h) for 7 days (up to 14 days in patients with a positive blood culture at baseline).

In patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m² and ≥ 30 mL/min/1.73 m²) the dose of FEP-EMT was adjusted to 1 g FEP plus 250 mg EMT, infused over a period of 2 hours q8h.

Arm type	Experimental
Investigational medicinal product name	Cefepime-Enmetazobactam
Investigational medicinal product code	FPE
Other name	Enmetazobactam = formerly AAI101
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study drug was prepared by an unblinded pharmacist (or qualified designee) according to the Pharmacy Manual. Cefepime-enmetazobactam was reconstituted in 20 mL normal saline (NS) and immediately mixed in the 250 mL saline bag for infusion. The i.v. bags were transferred to the blinded study staff for administration to the patient. At each administration of i.v. study drug, patients received a 270 mL infusion administered via a pump over a period of 2 hours.

In patients with moderate renal impairment (eGFR <60 mL/min/1.73 m² and ≥ 30 mL/min/1.73 m²) the dose of cefepime-enmetazobactam was adjusted to 1 g cefepime plus 250 mg enmetazobactam, infused over a period of 2 hours q8h.

Arm title	Piperacillin/Tazobactam
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Arm description:

4.5 g piperacillin/tazobactam infused over a period of 2 hours q8h for 7 days (up to 14 days in patients with a positive blood culture at baseline). Dosing of piperacillin/tazobactam followed the

recommendations as per the respective summary of product characteristics, which did not require adjustment of the 4.5 g dose in patients with mild or moderate renal impairment.

Arm type	Active comparator
Investigational medicinal product name	Piperacillin / Tazobactam
Investigational medicinal product code	
Other name	PipTazo
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosing of piperacillin/tazobactam followed the recommendations as per the respective summary of product characteristics, which did not require adjustment of the 4.5 g dose in patients with mild or moderate renal impairment.

Number of subjects in period 1	Cefepime- Enmetazobactam	Piperacillin/Tazobactam
Started	520	521
Completed	494	501
Not completed	26	20
Adverse event, serious fatal	-	3
Consent withdrawn by subject	7	6
Physician decision	-	1
Adverse event, non-fatal	3	2
Other	12	6
Lost to follow-up	3	2
Lack of efficacy	1	-

Baseline characteristics

Reporting groups

Reporting group title	Cefepime-Enmetazobactam
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Reporting group description:

2 g cefepime (FEP) plus 500 mg enmetazobactam (EMT) infused over a period of 2 hours once every 8 hours (q8h) for 7 days (up to 14 days in patients with a positive blood culture at baseline).
In patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m² and ≥ 30 mL/min/1.73 m²) the dose of FEP-EMT was adjusted to 1 g FEP plus 250 mg EMT, infused over a period of 2 hours q8h.

Reporting group title	Piperacillin/Tazobactam
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Reporting group description:

4.5 g piperacillin/tazobactam infused over a period of 2 hours q8h for 7 days (up to 14 days in patients with a positive blood culture at baseline). Dosing of piperacillin/tazobactam followed the recommendations as per the respective summary of product characteristics, which did not require adjustment of the 4.5 g dose in patients with mild or moderate renal impairment.

Reporting group values	Cefepime-Enmetazobactam	Piperacillin/Tazobactam	Total
Number of subjects	520	521	1041
Age categorical			
Units: Subjects			
Adults (18-64 years)	314	325	639
from 65-74 years	128	119	247
75 years and older	78	77	155
Age continuous			
Mean age			
Units: years			
arithmetic mean	55.0	54.3	-
standard deviation	± 18.97	± 19.13	
Gender categorical			
Units: Subjects			
Female	284	289	573
Male	236	232	468
Region			
Units: Subjects			
Eastern Europe	364	364	728
Americas	36	38	74
Other Countries	120	119	239
Type of Infection			
AP = Acute Pyelonephritis cUTI = complicated Urinary Tract Infection * ...but with other risk factors			
Units: Subjects			
AP	252	249	501
cUTI with removable source of infection	122	127	249
cUTI without removable source of infection*	146	145	291
Charlson Comorbidity Index (CCI) at Baseline			
Units: Subjects			

<3	311	307	618
>=3	202	202	404
not reported	7	12	19
Concurrent Bacteraemia at Baseline Units: Subjects			
Yes	41	30	71
No	479	491	970
Baseline Diabetic Status Units: Subjects			
Yes	79	78	157
No	441	443	884
eGFR (estimated glomerular filtration rate at Baseline) Units: mL/min/1.73m ² arithmetic mean standard deviation	72.91 ± 22.141	72.38 ± 24.759	-

Subject analysis sets

Subject analysis set title	ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT) Population included all patients who were randomized.	
Subject analysis set title	MITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The Modified Intent-to-Treat (MITT) Population included all patients who met ITT criteria and received any amount of study drug.	
Subject analysis set title	m-MITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The microbiological Modified Intention-to-treat (m-MITT) Population included all randomized patients who met MITT criteria and who had a baseline Gram-negative pathogen $\geq 10^5$ CFU/mL in urine culture or the same pathogen present in concurrent blood and urine cultures that caused the cUTI that was not resistant to cefepime-AAI101 (MIC determined with AAI101 at a fixed concentration of 8 µg/mL) or piperacillin/tazobactam (defined as MIC ≤ 8 µg/mL or MIC ≤ 64 µg/mL, respectively).	
Subject analysis set title	m-MITT+R Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: m-MITT+R Population included all randomized patients who met MITT criteria and who had a non-contaminated culture with a baseline Gram-negative pathogen $\geq 10^5$ CFU/mL in urine culture or the same pathogen present in concurrent blood and urine cultures that caused the cUTI, including isolates resistant to cefepime-AAI101 or piperacillin/tazobactam.	
Subject analysis set title	ME Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: The Microbiological Evaluable (ME) Population included patients who met the definition for both the m-MITT and the Clinically Evaluable (CE*) Populations. In addition, to have been included in the ME Population, patients must not have had a microbiological outcome at Test of Cure of Indeterminate. *The CE Population, defined as patients who met the MITT criteria as well as the specified criteria as detailed in the SAP, included 950 (91.3%) patients: 479 (92.1%) in the cefepime-AAI101 group and 471 (90.4%) patients in the piperacillin/tazobactam group.	
Subject analysis set title	ME+R Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ME+R Population included patients who met the definition for both the m-MITT+R and CE Populations. In addition, to be have been included in the ME+R Population, patients must not have had a microbiological outcome at TOC of Indeterminate.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Population included all patients who received at least 1 dose of study drug during the study. All safety analyses were based on actual treatment received.

Subject analysis set title	m-MITT Subgroup ESBL co-producing
Subject analysis set type	Sub-group analysis

Subject analysis set description:

m-MITT Subgroup ESBL co-producing

Subject analysis set title	m-MITT Subgroup ESBL-only producing
Subject analysis set type	Sub-group analysis

Subject analysis set description:

m-MITT Subgroup ESBL-only producing

Subject analysis set title	m-MITT Subgroup ESBL co-producing (CTX-M-type)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup ESBL co-producing (CTX-M-type)

Subject analysis set title	m-MITT Subgroup ESBL-only producing (CTX-M-type)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

m-MITT Subgroup ESBL-only producing (CTX-M-type)

Subject analysis set title	m-MITT Subgroup Non-ESBL-, non-carbapenemase-, non-AmpC-prod.
Subject analysis set type	Sub-group analysis

Subject analysis set description:

m-MITT Subgroup Non-ESBL-,non-carbapenemase-, and non-AmpC-producing

Reporting group values	ITT Population	MITT Population	m-MITT Population
Number of subjects	1041	1034	678
Age categorical			
Units: Subjects			
Adults (18-64 years)	639	636	429
from 65-74 years	247	244	155
75 years and older	155	154	94
Age continuous			
Mean age			
Units: years			
arithmetic mean	54.7	54.7	53.9
standard deviation	± 19.04	± 19.05	± 19.22
Gender categorical			
Units: Subjects			
Female	573	568	407
Male	468	466	271
Region			
Units: Subjects			
Eastern Europe	728	723	478
Americas	74	74	44
Other Countries	239	237	156

Type of Infection			
AP = Acute Pyelonephritis cUTI = complicated Urinary Tract Infection * ...but with other risk factors			
Units: Subjects			
AP	501	498	349
cUTI with removable source of infection	249	247	148
cUTI without removable source of infection*	291	289	181
Charlson Comorbidity Index (CCI) at Baseline			
Units: Subjects			
<3	618	618	403
>=3	404	404	270
not reported	19	12	5
Concurrent Bacteraemia at Baseline			
Units: Subjects			
Yes	71	71	66
No	970	963	612
Baseline Diabetic Status			
Units: Subjects			
Yes	157	157	96
No	884	877	582
eGFR (estimated glomerular filtration rate at Baseline)			
Units: mL/min/1.73m ²			
arithmetic mean	72.65	72.65	71.38
standard deviation	± 23.470	± 23.470	± 23.436

Reporting group values	m-MITT+R Population	ME Population	ME+R Population
Number of subjects	771	606	684
Age categorical			
Units: Subjects			
Adults (18-64 years)	487	385	435
from 65-74 years	176	140	158
75 years and older	108	81	91
Age continuous			
Mean age			
Units: years			
arithmetic mean	54.3	54.0	54.3
standard deviation	± 18.95	± 18.96	± 18.69
Gender categorical			
Units: Subjects			
Female	440	358	385
Male	331	248	299
Region			
Units: Subjects			
Eastern Europe	552	442	508
Americas	58	36	44
Other Countries	161	128	132
Type of Infection			
AP = Acute Pyelonephritis			

cUTI = complicated Urinary Tract Infection * ...but with other risk factors			
Units: Subjects			
AP	391	312	350
cUTI with removable source of infection	170	130	148
cUTI without removable source of infection*	210	164	186
Charlson Comorbidity Index (CCI) at Baseline			
Units: Subjects			
<3	462	357	410
>=3	302	246	270
not reported	7	3	4
Concurrent Bacteraemia at Baseline			
Units: Subjects			
Yes	71	51	56
No	700	555	628
Baseline Diabetic Status			
Units: Subjects			
Yes	112	88	99
No	659	518	585
eGFR (estimated glomerular filtration rate at Baseline)			
Units: mL/min/1.73m ²			
arithmetic mean	71.32	71.81	71.82
standard deviation	± 22.992	± 22.984	± 22.516

Reporting group values	Safety Population	m-MITT Subgroup ESBL co-producing	m-MITT Subgroup ESBL-only producing
Number of subjects	1034	142	137
Age categorical			
Units: Subjects			
Adults (18-64 years)	636		
from 65-74 years	244		
75 years and older	154		
Age continuous			
Mean age			
Units: years			
arithmetic mean	54.7		
standard deviation	± 19.05	±	±
Gender categorical			
Units: Subjects			
Female	568		
Male	466		
Region			
Units: Subjects			
Eastern Europe	723		
Americas	74		
Other Countries	237		
Type of Infection			
AP = Acute Pyelonephritis cUTI = complicated Urinary Tract Infection * ...but with other risk factors			

Units: Subjects			
AP	498		
cUTI with removable source of infection	247		
cUTI without removable source of infection*	289		
Charlson Comorbidity Index (CCI) at Baseline			
Units: Subjects			
<3	618		
>=3	404		
not reported	12		
Concurrent Bacteraemia at Baseline			
Units: Subjects			
Yes	71		
No	963		
Baseline Diabetic Status			
Units: Subjects			
Yes	157		
No	877		
eGFR (estimated glomerular filtration rate at Baseline)			
Units: mL/min/1.73m ²			
arithmetic mean	72.65		
standard deviation	± 23.470	±	±

Reporting group values	m-MITT Subgroup ESBL co-producing (CTX-M-type)	m-MITT Subgroup ESBL-only producing (CTX-M-type)	m-MITT Subgroup Non-ESBL-, non- carbapenemase-, non-AmpC-prod.
Number of subjects	141	133	26
Age categorical			
Units: Subjects			
Adults (18-64 years)			
from 65-74 years			
75 years and older			
Age continuous			
Mean age			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			
Region			
Units: Subjects			
Eastern Europe			
Americas			
Other Countries			
Type of Infection			
AP = Acute Pyelonephritis cUTI = complicated Urinary Tract Infection * ...but with other risk factors			

Units: Subjects			
AP cUTI with removable source of infection cUTI without removable source of infection*			
Charlson Comorbidity Index (CCI) at Baseline Units: Subjects			
<3 ≥3 not reported			
Concurrent Bacteraemia at Baseline Units: Subjects			
Yes No			
Baseline Diabetic Status Units: Subjects			
Yes No			
eGFR (estimated glomerular filtration rate at Baseline) Units: mL/min/1.73m ² arithmetic mean standard deviation	±	±	±

End points

End points reporting groups

Reporting group title	Cefepime-Enmetazobactam
Reporting group description: 2 g cefepime (FEP) plus 500 mg enmetazobactam (EMT) infused over a period of 2 hours once every 8 hours (q8h) for 7 days (up to 14 days in patients with a positive blood culture at baseline). In patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m ² and ≥ 30 mL/min/1.73 m ²) the dose of FEP-EMT was adjusted to 1 g FEP plus 250 mg EMT, infused over a period of 2 hours q8h.	
Reporting group title	Piperacillin/Tazobactam
Reporting group description: 4.5 g piperacillin/tazobactam infused over a period of 2 hours q8h for 7 days (up to 14 days in patients with a positive blood culture at baseline). Dosing of piperacillin/tazobactam followed the recommendations as per the respective summary of product characteristics, which did not require adjustment of the 4.5 g dose in patients with mild or moderate renal impairment.	
Subject analysis set title	ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT) Population included all patients who were randomized.	
Subject analysis set title	MITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The Modified Intent-to-Treat (MITT) Population included all patients who met ITT criteria and received any amount of study drug.	
Subject analysis set title	m-MITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The microbiological Modified Intention-to-treat (m-MITT) Population included all randomized patients who met MITT criteria and who had a baseline Gram-negative pathogen $\geq 10^5$ CFU/mL in urine culture or the same pathogen present in concurrent blood and urine cultures that caused the cUTI that was not resistant to cefepime-AAI101 (MIC determined with AAI101 at a fixed concentration of 8 µg/mL) or piperacillin/tazobactam (defined as MIC ≤ 8 µg/mL or MIC ≤ 64 µg/mL, respectively).	
Subject analysis set title	m-MITT+R Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: m-MITT+R Population included all randomized patients who met MITT criteria and who had a non-contaminated culture with a baseline Gram-negative pathogen $\geq 10^5$ CFU/mL in urine culture or the same pathogen present in concurrent blood and urine cultures that caused the cUTI, including isolates resistant to cefepime-AAI101 or piperacillin/tazobactam.	
Subject analysis set title	ME Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: The Microbiological Evaluable (ME) Population included patients who met the definition for both the m-MITT and the Clinically Evaluable (CE*) Populations. In addition, to have been included in the ME Population, patients must not have had a microbiological outcome at Test of Cure of Indeterminate. *The CE Population, defined as patients who met the MITT criteria as well as the specified criteria as detailed in the SAP, included 950 (91.3%) patients: 479 (92.1%) in the cefepime-AAI101 group and 471 (90.4%) patients in the piperacillin/tazobactam group.	
Subject analysis set title	ME+R Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: ME+R Population included patients who met the definition for both the m-MITT+R and CE Populations. In addition, to have been included in the ME+R Population, patients must not have had a microbiological outcome at TOC of Indeterminate.	

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Population included all patients who received at least 1 dose of study drug during the study. All safety analyses were based on actual treatment received.	
Subject analysis set title	m-MITT Subgroup ESBL co-producing
Subject analysis set type	Sub-group analysis
Subject analysis set description: m-MITT Subgroup ESBL co-producing	
Subject analysis set title	m-MITT Subgroup ESBL-only producing
Subject analysis set type	Sub-group analysis
Subject analysis set description: m-MITT Subgroup ESBL-only producing	
Subject analysis set title	m-MITT Subgroup ESBL co-producing (CTX-M-type)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup ESBL co-producing (CTX-M-type)	
Subject analysis set title	m-MITT Subgroup ESBL-only producing (CTX-M-type)
Subject analysis set type	Sub-group analysis
Subject analysis set description: m-MITT Subgroup ESBL-only producing (CTX-M-type)	
Subject analysis set title	m-MITT Subgroup Non-ESBL-, non-carbapenemase-, non-AmpC-prod.
Subject analysis set type	Sub-group analysis
Subject analysis set description: m-MITT Subgroup Non-ESBL-,non-carbapenemase-, and non-AmpC-producing	

Primary: Overall Response at TOC - m-MITT Population

End point title	Overall Response at TOC - m-MITT Population
End point description: The primary efficacy parameter was the proportion of patients in the m-MITT Population (678 patients) who achieved overall treatment success at TOC. Overall treatment success was defined as the composite of clinical outcome of Cure and the microbiological outcome of Eradication (<10 ³ CFU/mL in urine culture). The majority of patients in the cefepime-enmetazobactam group (273 [79.1%] patients) had an overall response of success at TOC compared to the piperacillin/tazobactam group (196 [58.9%] patients), with a treatment difference of 21.2% (95% CI: 14.3, 27.9), demonstrating superiority of cefepime-enmetazobactam compared to piperacillin/tazobactam.	
End point type	Primary
End point timeframe: Table summarizes the primary efficacy analysis of overall response at Test-of-Cure (TOC) Visit for the m-MITT Population.	

End point values	Cefepime-Enmetazobactam	Piperacillin/Tazobactam	m-MITT Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	345	333	678	
Units: Number of Subjects				
Success	273	196	469	
Failure	51	116	167	

Indeterminate	21	21	42	
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Attachments (see zip file)	Forest Overall Success at TOC_m-MITT.pdf
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Statistical analyses

Statistical analysis title	Treatment Difference in Overall Success
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Statistical analysis description:

The non-inferiority assessment was based on the stratified Newcombe 2-sided 95% confidence interval (CI) for the difference in the proportions of patients with overall treatment successes, calculated as the rate in the cefepime-AAI101 group minus that of the piperacillin/tazobactam group. The non-inferiority margin was a difference of 10 percentage points. Non-inferiority was concluded if the lower limit of the 2-sided 95% CI was >-10 .

Comparison groups	Cefepime-Enmetazobactam v Piperacillin/Tazobactam
Number of subjects included in analysis	678
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	21.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.3
upper limit	27.9

Statistical analysis title	Treatment Difference in Overall Success Sup
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Statistical analysis description:

If non-inferiority was demonstrated, an assessment for superiority on the primary endpoint was performed as a secondary objective without the need for type I error alpha correction. Superiority was shown if the treatment difference was positive and the lower bound of the 95% CI around this difference was greater than zero.

Comparison groups	Cefepime-Enmetazobactam v Piperacillin/Tazobactam
Number of subjects included in analysis	678
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	21.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.3
upper limit	27.9

Primary: Overall Response at TOC - m-MITT+R Population

End point title	Overall Response at TOC - m-MITT+R Population
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End point description:

In the m-MITT+R population, the majority of patients in the cefepime-enmetazobactam group (305 [78.6%] patients) had an overall response of success at TOC compared to the piperacillin/tazobactam group (225 [58.7%] patients) with a treatment difference of 20.7% (95% CI: 14.1, 27.0), demonstrating superiority of cefepime-enmetazobactam compared to piperacillin/tazobactam.

End point type	Primary
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End point timeframe:

Table summarizes the primary efficacy analysis of overall response at Test-of-Cure (TOC) Visit for the m-MITT+R Population.

End point values	Cefepime-Enmetazobactam	Piperacillin/Tazobactam	m-MITT Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	388	383	771	
Units: Number of Subjects				
Success	305	225	530	
Failure	58	128	186	
Indeterminate	25	30	55	

Statistical analyses

Statistical analysis title	Treatment Difference in Overall Success
Comparison groups	Cefepime-Enmetazobactam v Piperacillin/Tazobactam
Number of subjects included in analysis	771
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	20.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.1
upper limit	27

Statistical analysis title	Treatment Difference in Overall Success Sup
Comparison groups	Cefepime-Enmetazobactam v Piperacillin/Tazobactam

Number of subjects included in analysis	771
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	20.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.1
upper limit	27

Secondary: Overall Response at Other Timepoints - m-MITT Population - Categorical

End point title	Overall Response at Other Timepoints - m-MITT Population - Categorical
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End point description:

Descriptive statistics are provided for secondary efficacy endpoints.

End point type	Secondary
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End point timeframe:

This table summarizes the proportion of patients with overall response at Day 3, End of Treatment, and Late Follow-up for the m-MITT Population.

End point values	Cefepime- Enmetazobactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	333		
Units: Number of Subjects				
Day 3 - Success	318	293		
Day 3 - Failure	16	24		
Day 3- Indeterminate	11	16		
End of Treatment - Success	318	311		
End of Treatment - Failure	12	12		
End of Treatment - Indeterminate	15	10		
Late Follow-up - Success	236	196		
Late Follow-up - Failure	88	113		
Late Follow-up - Indeterminate	21	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response at Other Timepoints - m-MITT Population - Treatment Comparison

End point title	Overall Response at Other Timepoints - m-MITT Population -
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End point description:

Descriptive statistics are provided for secondary efficacy endpoints.

At Day 3, the treatment difference between the two arms was 4.1% (95% CI: -0.6, 8.9) demonstrating non-inferiority of cefepime-enmetazobactam compared to piperacillin/tazobactam.

At End of Treatment, the treatment difference between the two arms was -1.3% (95% CI: -5.3, 2.9) demonstrating non-inferiority of cefepime-enmetazobactam compared to piperacillin/tazobactam.

At Late Follow-up, the treatment difference between the two arms was 10.7% (95% CI: 3.4, 17.8) demonstrating superiority of cefepime-enmetazobactam compared to piperacillin/tazobactam.

End point type	Secondary
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End point timeframe:

Table shows the treatment differences in the m-MITT population between the two arms at Day 3, End of Treatment, and Late Follow-up.

End point values	m-MITT Population			
Subject group type	Subject analysis set			
Number of subjects analysed	678			
Units: Difference (%)				
arithmetic mean (confidence interval 95%)				
Day 3	4.1 (-0.6 to 8.9)			
End of Treatment	-1.3 (-5.3 to 2.9)			
Late Follow-up	10.7 (3.4 to 17.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological Response - m-MITT Population - Categorical

End point title	Microbiological Response - m-MITT Population - Categorical
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End point description:

Descriptive statistics are provided for secondary efficacy endpoints.

At Day 3, End of Treatment, Test of Cure, and Late Follow-up, the majority of patients in both treatment groups had a microbiological response of Eradication: 323 (93.6%), 332 (96.2%), 286 (82.9%), and 258 (74.8%) patients, respectively, in the cefepime-enmetazobactam group; and 299 (89.8%), 322 (96.7%), 216 (64.9%), and 221 (66.4%) patients, respectively, in the piperacillin/tazobactam group.

End point type	Secondary
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End point timeframe:

Table summarizes the proportion of patients with a microbiological response by visit for the m-MITT Population.

End point values	Cefepime-Enmetazobactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	333		
Units: Number of Subjects				
Day 3 - Eradication	323	299		
Day 3 - Persistence	11	21		
Day 3 - Indeterminate	11	13		
End of Treatment - Eradication	332	322		
End of Treatment - Persistence	1	2		
End of Treatment - Recurrence	1	1		
End of Treatment - Indeterminate	11	8		
Test of Cure - Eradication	286	216		
Test of Cure - Persistence	1	2		
Test of Cure - Recurrence	39	98		
Test of Cure - Indeterminate	19	17		
Late Follow-up - Eradication	258	221		
Late Follow-up - Persistence	1	1		
Late Follow-up - Recurrence	71	90		
Late Follow-up - Indeterminate	15	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological Response - m-MITT Population - Treatment Comparison

End point title	Microbiological Response - m-MITT Population - Treatment Comparison
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End point description:

Descriptive statistics are provided for secondary efficacy endpoints.

A treatment difference of 3.8% (95% CI: -0.6, 8.3), -0.7% (95% CI: -3.7, 2.5), 19.0% (95% CI: 12.3, 25.4), and 9.5% (95% CI: 2.6, 16.3) was observed between the cefepime-enmetazobactam group and the piperacillin/tazobactam group at Day 3, EOT, TOC, and LFU, respectively. The treatment difference demonstrated superiority of cefepime-enmetazobactam compared to piperacillin/tazobactam at TOC and LFU, and non-inferiority of cefepime-enmetazobactam compared to piperacillin/tazobactam at Day 3 and EOT.

EOT = End of Treatment; TOC = Test of Cure; LFU = Late Follow-up.

End point type	Secondary
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End point timeframe:

Table shows treatment difference in the microbiological response between the two arms at Day 3, End-of-Treatment, Test-of-Cure, and Late Follow-up.

End point values	m-MITT Population			
Subject group type	Subject analysis set			
Number of subjects analysed	678			
Units: Difference (%)				
arithmetic mean (confidence interval 95%)				
Day 3	3.8 (-0.6 to 8.3)			
End-of-Treatment	-0.7 (-3.7 to 2.5)			
Test-of-Cure	19.0 (12.3 to 25.4)			
Late Follow-up	9.5 (2.6 to 16.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Response - m-MITT Population - Categorical

End point title	Clinical Response - m-MITT Population - Categorical
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End point description:

Descriptive statistics are provided for secondary efficacy endpoints.

At Day 3, End of Treatment, Test of Cure, and Late Follow-up, the majority of patients in both treatment groups had a clinical response of Cure: 323 (93.6%), 319 (92.5%), and 299 (86.7%) patients, respectively, in the cefepime-enmetazobactam group; and 315 (94.6%), 296 (88.9%), and 279 (83.8%) patients, respectively, in the piperacillin/tazobactam group.

End point type	Secondary
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End point timeframe:

Table summarizes the proportion of patients with a clinical response by visit for the m-MITT Population.

End point values	Cefepime-Enmetazobactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	333		
Units: Number of Subjects				
Day 3 - Cure	18	16		
Day 3 - Improvement	317	302		
Day 3 - Failure	5	4		
Day 3 - Indeterminate	5	11		
End of Treatment - Cure	323	315		
End of Treatment - Improvement	2	1		
End of Treatment - Failure	10	9		
End of Treatment - Indeterminate	10	8		
Test of Cure - Cure	319	296		
Test of Cure - Failure	17	23		
Test of Cure - Indeterminate	9	14		

Late Follow-up - Cure	299	279		
Late Follow-up - Failure	25	39		
Late Follow-up - Indeterminate	21	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Response - m-MITT Population - Treatment Comparison

End point title	Clinical Response - m-MITT Population - Treatment Comparison
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End point description:

Descriptive statistics are provided for secondary efficacy endpoints.

A treatment difference of -1.1% (95% CI: -4.8, 2.7), 3.5% (95% CI: -1.0, 8.0), and 2.8% (95% CI: -2.7, 8.3) was observed between the cefepime-enmetazobactam group and the piperacillin/tazobactam group at EOT, TOC, and LFU, respectively. The treatment difference demonstrated non-inferiority of cefepime-enmetazobactam compared to piperacillin/tazobactam at EOT, TOC, and LFU.

EOT = End of Treatment; TOC = Test of Cure; LFU = Late Follow-up.

End point type	Secondary
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End point timeframe:

Table shows treatment difference in the clinical response between the two arms at Day 3, End-of-Treatment, Test-of-Cure, and Late Follow-up.

End point values	m-MITT Population			
Subject group type	Subject analysis set			
Number of subjects analysed	678			
Units: Difference (%)				
arithmetic mean (confidence interval 95%)				
Day 3	0.5 (-3.1 to 4.0)			
End of Treatment	-1.1 (-4.8 to 2.7)			
Test of Cure	3.5 (-1.0 to 8.0)			
Late Follow-up	2.8 (-2.7 to 8.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: ESBL Subgroup Analysis at Test of Cure - m-MITT Population

End point title	ESBL Subgroup Analysis at Test of Cure - m-MITT Population
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End point description:

Descriptive statistics are provided here.

For overall response of success* at TOC Visit, the subgroups of patients with ESBL co-producing (ESBL-genotype, combined with or without any other non-ESBL genotype), ESBL-only producing, ESBL co-producing (CTX-M-type), and ESBL-only producing (CTX-M-type) at baseline had a treatment difference that demonstrated superiority of cefepime-AAI101 compared to piperacillin/tazobactam. The following sub-groups were not evaluable due to low numbers: ESBL co-producing (non-CTX-M-type), ESBL-only producing (non-CTX-M-type), AmpC co-producing, AmpC-only producing.

Results of the subgroup analysis of overall response for all ESBL-producing isolates of enterobacteriaceae subgroups at TOC Visit (m-MITT Population) is provided in the attached table, together with a Forest Plot illustrating overall success at TOC Visit by various subgroups.

*Overall Success was defined as clinical cure or improvement and microbiological eradication.

End point type	Secondary
End point timeframe:	
Table summarizes the treatment differences for success within the ESBL subgroup analysis of overall response at Test-of-Cure Visit.	

End point values	m-MITT Subgroup ESBL co-producing	m-MITT Subgroup ESBL-only producing	m-MITT Subgroup ESBL co-producing (CTX-M-type)	m-MITT Subgroup ESBL-only producing (CTX-M-type)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	142	137	141	133
Units: Difference (%)				
arithmetic mean (confidence interval 95%)				
Difference (%)	30.2 (13.4 to 45.1)	31.8 (14.6 to 46.6)	30.8 (13.9 to 45.7)	32.6 (15.3 to 47.6)

End point values	m-MITT Subgroup Non-ESBL-, non-carbapenemas e-, non-AmpC-prod.			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: Difference (%)				
arithmetic mean (confidence interval 95%)				
Difference (%)	11.5 (-23.0 to 43.8)			

Attachments (see zip file)	Forest Plot of Microbiological Eradication/Forest Microbio
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events for the Safety Population are documented from the time of first study drug administration until completion of study participation.

Adverse event reporting additional description:

The safety and tolerability profile was determined by incidence and severity of Adverse Events and Serious Adverse Events, vital signs, laboratory tests, ECGs, and physical examinations from Screening through Late Follow-Up (End of Treatment + 14 days [± 2 days]).

Threshold for non-serious adverse event reporting is: 2%

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Cefepime / Enmetazobactam Treatment Arm
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Reporting group description:

This reporting group includes all patients in the Safety Population who received at least one dose of Cefepime / Enmetazobactam.

The total number of subjects affected by any non-serious adverse events in this safety population is 258. Number of subjects reported here corresponds to non-serious adverse events with an occurrence of $\geq 2\%$.

Reporting group title	Piperacillin / Tazobactam Treatment Arm
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Reporting group description:

This reporting group includes all patients in the Safety Population who received at least one dose of Piperacillin / Tazobactam

The total number of subjects affected by any non-serious adverse events in this safety population is 228. Number of subjects reported here corresponds to non-serious adverse events with an occurrence of $\geq 2\%$.

Serious adverse events	Cefepime / Enmetazobactam Treatment Arm	Piperacillin / Tazobactam Treatment Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 516 (4.26%)	19 / 518 (3.67%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events	3	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung cancer metastatic			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung carcinoma cell type unspecified recurrent			

subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	2 / 516 (0.39%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Nephrectomy			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (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			
Bladder neck obstruction			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haematoma			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (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			
Clostridium difficile colitis			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epididymitis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 516 (0.39%)	2 / 518 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	4 / 516 (0.78%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
subjects affected / exposed	0 / 516 (0.00%)	2 / 518 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 516 (0.00%)	1 / 518 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal infection			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic shock syndrome			
subjects affected / exposed	1 / 516 (0.19%)	0 / 518 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 516 (0.39%)	3 / 518 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cefepime / Enmetazobactam Treatment Arm	Piperacillin / Tazobactam Treatment Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	238 / 516 (46.12%)	215 / 518 (41.51%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	59 / 516 (11.43%)	60 / 518 (11.58%)	
occurrences (all)	59	60	
Aspartate aminotransferase increased			
subjects affected / exposed	47 / 516 (9.11%)	46 / 518 (8.88%)	
occurrences (all)	47	46	
Blood bilirubin increased			
subjects affected / exposed	30 / 516 (5.81%)	20 / 518 (3.86%)	
occurrences (all)	30	20	
Transaminases increased			
subjects affected / exposed	13 / 516 (2.52%)	19 / 518 (3.67%)	
occurrences (all)	13	19	
Vascular disorders			
Phlebitis			
subjects affected / exposed	14 / 516 (2.71%)	1 / 518 (0.19%)	
occurrences (all)	14	1	
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 516 (4.84%)	12 / 518 (2.32%)	
occurrences (all)	25	12	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 516 (2.52%)	15 / 518 (2.90%)	
occurrences (all)	13	15	
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	21 / 516 (4.07%) 21	26 / 518 (5.02%) 26	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	5 / 516 (0.97%) 5	8 / 518 (1.54%) 8	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	11 / 516 (2.13%) 11	8 / 518 (1.54%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2018	<p>Amendment no.1: Piperacillin/tazobactam was selected to be used as a comparator in this complicated urinary tract infection (cUTI) trial due to its antibacterial spectrum, its pharmacokinetic properties and due to the fact that it is a beta-lactam/beta-lactamase inhibitor combination very similar to the cefepime/AAI101 combination.</p> <p>Inclusion Criterion 3 was revised to define permanent sterilization for women who are no longer of childbearing potential. A new Exclusion Criterion 1 was added to exclude patients who have qualifying Gram-positive primary pathogen at $\geq 10^5$ colony-forming units (CFU)/mL. Exclusion Criterion 2 was revised to reflect piperacillin/tazobactam as the comparator drug. Exclusion Criterion 7 was revised to define the exceptions to the receipt of potentially effective systemic antibacterial therapy for continuous duration of >24 hours during the previous 72 hours before study-qualifying baseline urine is collected. Exclusion Criterion 10 was adjusted to match the extended duration of treatment. Exclusion Criterion 15 was revised to note glomerular filtration rate rather than creatinine clearance. Exclusion Criterion 25 was revised to further define the time prior to Screening regarding the administration of experimental medication.</p> <p>Piperacillin/tazobactam will be administered over a period of 2 hours once every 8 hours (q8h) for 7 days. Possible treatment duration was extended from 7 to 10 days to 7 to 14 days in patients with a positive blood culture at baseline. The criteria for microbiological outcome were revised.</p> <p>Prothrombin and partial thromboplastin time were added to clinical laboratory assessments.</p> <p>The number of sites was reduced from 120 to 115.</p> <p>The schedule of procedures and clinical laboratory analytes was updated to reflect the changes specified herein, where applicable. Other minor edits were made throughout the document to improve clarity, consistency, and to correct grammatical errors.</p>
19 June 2018	<p>Amendment no.2: This amendment was developed in response to Food and Drug Administration (FDA) feedback during the end of Phase 2 meeting and a review of the amended protocol. Other minor edits were made throughout the document to correct grammatical errors and inconsistencies.</p> <p>The study population was updated to specify that at least 50% of patients will have complicated urinary tract infection (cUTI) and at least 30% will have acute pyelonephritis (AP).</p> <p>Exclusion Criterion 15 was revised to specify that patients with impairment of renal function with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² are excluded from the study. In Exclusion Criterion 22, it was specified that patients with current clinically significant liver disease, including any form of known liver cirrhosis are also excluded from the study.</p> <p>Dosing in patients with renal insufficiency was updated to be consistent with Exclusion Criterion 15.</p> <p>It was specified that a triplicate 12-lead electrocardiogram (ECG) will be performed at Screening and Day 4.</p> <p>It was clarified that up to 2 Gram-negative bacterial isolates per urine culture (at concentrations of $\geq 10^5$ CFU/mL of urine) will be considered as qualifying pathogens.</p> <p>The overall response to a clinical outcome of Cure and microbiological outcome of Indeterminate was updated to Indeterminate.</p> <p>Secondary efficacy parameters were updated to include additional subsets of patients.</p> <p>Protocol Section was added to clarify adverse events of special interest.</p> <p>Sample size determination was revised.</p> <p>Direct bilirubin and C-reactive protein were added to the clinical laboratory analysis.</p> <p>The relevant protocol tables and schedule of procedures were updated to reflect the changes specified herein, where applicable.</p>

02 August 2018	<p>Amendment no.3: This amendment was developed in response to Food and Drug Administration feedback during the end of Phase 2 meeting and a review of the amended protocol. Other minor edits were made throughout the document to correct grammatical errors and inconsistencies.</p> <p>Inclusion Criterion 7 was updated to clarify that if the patient has met the criteria for complicated urinary tract infection (cUTI) and acute pyelonephritis (AP), the infection type would be considered cUTI for randomization and analysis purposes. Collection of blood samples for PK analysis was clarified for Day 7 and the Early Termination visit.</p> <p>A Study Scheme figure was added.</p> <p>Dosing in patients with renal insufficiency was updated to clarify confirmation for patients with normal renal function or mild or moderate renal impairment at baseline.</p> <p>Collection of laboratory assessments was updated to clarify collections on Day 7; Days 8, 9, 11, 12, or 13; and Day 10.</p> <p>Adverse events of special interest were updated for the new laboratory assessment collected on Day 10.</p> <p>Criteria for study drug discontinuation were updated.</p> <p>Expedited reporting was clarified.</p> <p>The relevant protocol tables and schedule of procedures were updated to reflect the changes specified herein, where applicable.</p>
06 September 2018	<p>Amendment no.4: This amendment was developed in response to Food and Drug Administration feedback during the End of Phase 2 meeting and a review of the amended protocol. Other minor edits were made throughout the document to correct grammatical errors and inconsistencies.</p> <p>Study design was updated to include that the Test of Cure (TOC) visit will occur 7 days after End of Treatment (EOT) (EOT + 7 days [± 2 days]) for patients receiving 7 days of treatment and 19 days after randomization (randomization + 19 days [± 2 days]) for patients receiving more than 7 days of treatment. The Late Follow-up (LFU) visit was also updated to clarify that the LFU visit should not take place earlier than 3 days after the TOC visit.</p> <p>It was specified that for patients without bacteremia, treatment cannot be prolonged for more than 7 days.</p> <p>The blood samples collection time for laboratory assessments on Day 1 was clarified.</p> <p>It was clarified that in patients with moderate renal impairment, dose adjustment is applicable from Day 1 of dosing.</p> <p>Direct bilirubin was removed from the screening laboratory assessments for eligibility.</p> <p>The relevant protocol tables and schedule of procedures were updated to reflect the changes specified herein, where applicable.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported