Clinical trial results:
A Phase 2a, 2-part, Open-label, Non-randomized, Multicenter, Single and Multiple Dose Trial to Evaluate Pharmacokinetics, Safety and Tolerability of Ceftazidime and Avibactam in Neonates and Infants from Birth to Less than 3 Months of Age with Suspected or Confirmed Infections Due to Gram-negative Pathogens Requiring Intravenous Antibiotic Treatment

Summary

EudraCT number	2018-002800-16
Trial protocol	SK HU EE GR IT
Global end of trial date	23 July 2022

Results information

Result version number	v1 (current)
This version publication date	15 July 2023
First version publication date	15 July 2023

Trial information

Trial identification

Sponsor protocol code	C3591024

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04126031
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001313-PIP01-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 July 2022
Global end of trial reached?	Yes
Global end of trial date	23 July 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To characterize the pharmacokinetics (PK) of a single intravenous dose of CAZ-AVI in hospitalized neonates and infants from birth to less than 3 months.
To evaluate the safety and tolerability of a single intravenous dose of CAZ-AVI in hospitalized neonates and infants from birth to less than 3 months.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 2020
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	Hungary: 3
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Greece: 17
Worldwide total number of subjects	46
EEA total number of subjects	35

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	15
Newborns (0-27 days)	12
Infants and toddlers (28 days-23	19

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 52 subjects were screened, 4 subjects were screen failures and 48 were enrolled to the study. 27 subjects in Part A and 21 subjects in Part B. Out of which 2 subjects were not treated from Part A. 46 subjects were assigned to a treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Cohort 1

Arm description:

On Day 1 subjects aged 28days to less than (<) 3 months old received a single intravenous (IV) infusion of ceftazidime-avibactam (CAZ-AVI) 30 milligrams per kilogram (mg/kg) CAZ and 7.5 mg/kg AVI over a 2-hour (+/-10 min) period.

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

Dosage and administration details:

7.5 mg/kg

Investigational medicinal product name	Ceftazidime
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/kg

Arm title	Part A: Cohort 2

Arm description:

On Day 1 subjects aged greater than or equal to(>=) 37weeks and less than or equal to (<=) 28 days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period.

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

Dosage and administration details:

5 mg/kg

Investigational medicinal product name	Ceftazidime
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg

Arm title	Part A: Cohort 3

Arm description:

On Day 1 subjects aged >=26 week to <37week and <=28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period.

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

Dosage and administration details:

20 mg/kg

Investigational medicinal product name	Avibactam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg

Arm title	Part B: Cohort 1

Arm description:

On Day 1 subjects aged 28days to <3 months old received a single IV infusion of CAZ-AVI 30 milligrams per kilogram (mg/kg) CAZ and 7.5 mg/kg AVI over a 2-hour (+/-10 min) period every 8 hours (+/-1 hour).

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

Dosage and administration details:

7.5 mg/kg

Investigational medicinal product name	Ceftazidime
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/kg

Arm title	Part B: Cohort 2

Arm description:

On Day 1 subjects aged >= 37week and <= 28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over 2-hour (+/-10 min) period every 8 hours (+/-1 hour).

Arm type	Experimental

Investigational medicinal product name	Avibactam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg

Investigational medicinal product name	Ceftazidime
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg

Arm title	Part B: Cohort 3

Arm description:

On Day 1 subjects aged >=26week to <37week and <=28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period every 8 hours (+/-1 hour).

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

Dosage and administration details:

5 mg/kg

Investigational medicinal product name	Ceftazidime
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg

Number of subjects in period 1	Part A: Cohort 1	Part A: Cohort 2	Part A: Cohort 3
Started	9	8	8
Completed	9	8	8

Number of subjects in period 1	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3
Started	8	5	8
Completed	8	5	8

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Cohort 1
Reporting group description:	
On Day 1 subjects aged 28days to less than (<) 3 months old received a single intravenous (IV) infusion of ceftazidime-avibactam (CAZ-AVI) 30 milligrams per kilogram (mg/kg) CAZ and 7.5 mg/kg AVI over a 2-hour (+/-10 min) period.	
Reporting group title	Part A: Cohort 2
Reporting group description:	
On Day 1 subjects aged greater than or equal to(>=) 37weeks and less than or equal to (<=) 28 days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period.	
Reporting group title	Part A: Cohort 3
Reporting group description:	
On Day 1 subjects aged >=26 week to <37week and <=28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period.	
Reporting group title	Part B: Cohort 1
Reporting group description:	
On Day 1 subjects aged 28days to <3 months old received a single IV infusion of CAZ-AVI 30 milligrams per kilogram (mg/kg) CAZ and 7.5 mg/kg AVI over a 2-hour (+/-10 min) period every 8 hours (+/-1 hour).	
Reporting group title	Part B: Cohort 2
Reporting group description:	
On Day 1 subjects aged >= 37week and <= 28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over 2-hour (+/-10 min) period every 8 hours (+/-1 hour).	
Reporting group title	Part B: Cohort 3
Reporting group description:	
On Day 1 subjects aged >=26week to <37week and <=28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period every 8 hours (+/-1 hour).	

Reporting group values	Part A: Cohort 1	Part A: Cohort 2	Part A: Cohort 3
Number of subjects	9	8	8
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	8
Newborns (0-27 days)	0	7	0
Infants and toddlers (28 days-23 months)	9	1	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	59.0	19.3	14.6
standard deviation	± 15.73	± 9.00	± 7.46

Sex: Female, Male Units: Participants			
Female	5	4	6
Male	4	4	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	0
White	6	5	7
More than one race	0	0	0
Unknown or Not Reported	0	0	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	7	7	7
Unknown or Not Reported	1	1	0

Reporting group values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3
Number of subjects	8	5	8
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	7
Newborns (0-27 days)	0	5	0
Infants and toddlers (28 days-23 months)	8	0	1
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	51.1	15.8	17.8
standard deviation	± 18.16	± 7.63	± 8.99
Sex: Female, Male Units: Participants			
Female	3	1	6
Male	5	4	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	0	0
White	5	5	8
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	8	5	8
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	46		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	15		
Newborns (0-27 days)	12		
Infants and toddlers (28 days-23 months)	19		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	25		
Male	21		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	5		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	4		
White	36		
More than one race	0		
Unknown or Not Reported	1		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	42		
Unknown or Not Reported	2		

End points

End points reporting groups

Reporting group title	Part A: Cohort 1
Reporting group description:	
On Day 1 subjects aged 28days to less than (<) 3 months old received a single intravenous (IV) infusion of ceftazidime-avibactam (CAZ-AVI) 30 milligrams per kilogram (mg/kg) CAZ and 7.5 mg/kg AVI over a 2-hour (+/-10 min) period.	
Reporting group title	Part A: Cohort 2
Reporting group description:	
On Day 1 subjects aged greater than or equal to(>=) 37weeks and less than or equal to (<=) 28 days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period.	
Reporting group title	Part A: Cohort 3
Reporting group description:	
On Day 1 subjects aged >=26 week to <37week and <=28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period.	
Reporting group title	Part B: Cohort 1
Reporting group description:	
On Day 1 subjects aged 28days to <3 months old received a single IV infusion of CAZ-AVI 30 milligrams per kilogram (mg/kg) CAZ and 7.5 mg/kg AVI over a 2-hour (+/-10 min) period every 8 hours (+/-1 hour).	
Reporting group title	Part B: Cohort 2
Reporting group description:	
On Day 1 subjects aged >= 37week and <= 28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over 2-hour (+/-10 min) period every 8 hours (+/-1 hour).	
Reporting group title	Part B: Cohort 3
Reporting group description:	
On Day 1 subjects aged >=26week to <37week and <=28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period every 8 hours (+/-1 hour).	

Primary: Plasma Concentrations of Ceftazidime and Avibactam 2 Hours Post-dose: Part A

End point title	Plasma Concentrations of Ceftazidime and Avibactam 2 Hours Post-dose: Part A[1][2]
End point description:	
The Pharmacokinetic (PK) analysis set for Part A was defined as subjects who received a single IV dose of CAZ-AVI in Part A.	
End point type	Primary
End point timeframe:	
2 hours post-dose on Day 1	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part A: Cohort 1	Part A: Cohort 2	Part A: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	8	
Units: Nanogram per milliliter				
arithmetic mean (standard deviation)				
Ceftazidime	104544.4 (± 113161.34)	35537.5 (± 13473.88)	53212.5 (± 25972.32)	
Avibactam	19210.0 (± 18747.86)	6910.0 (± 2553.50)	10570.0 (± 4342.69)	

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentrations of Ceftazidime and Avibactam 2 Hours and 30 Minutes Post-dose: Part A

End point title	Plasma Concentrations of Ceftazidime and Avibactam 2 Hours and 30 Minutes Post-dose: Part A[3][4]

End point description:

PK analysis set for Part A was defined as subjects who received a single IV dose of CAZ-AVI in Part A.

End point type	Primary

End point timeframe:

2 hours and 30 minutes post-dose on Day 1

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part A: Cohort 1	Part A: Cohort 2	Part A: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	7	8	
Units: Nanogram per milliliter				
arithmetic mean (standard deviation)				
Ceftazidime	76822.2 (± 106423.76)	32571.4 (± 10842.00)	49012.5 (± 18832.45)	
Avibactam	13250.0 (± 16906.67)	6251.4 (± 2363.99)	9788.8 (± 2956.39)	

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentrations of Ceftazidime and Avibactam 7 Hours Post-dose: Part A

End point title	Plasma Concentrations of Ceftazidime and Avibactam 7 Hours

	Post-dose: Part A[5][6]

End point description:

PK analysis set for Part A was defined as subjects who received a single IV dose of CAZ-AVI in Part A.

End point type	Primary

End point timeframe:

7 hours post dose on Day 1

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part A: Cohort 1	Part A: Cohort 2	Part A: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	8	
Units: Nanogram per milliliter				
arithmetic mean (standard deviation)				
Ceftazidime	15635.6 (± 15243.22)	8305.0 (± 6728.50)	17608.8 (± 8165.42)	
Avibactam	2058.2 (± 1670.32)	1190.4 (± 998.69)	3475.6 (± 1931.10)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs): Part B

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs): Part B[7][8]

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-subject hospitalization; life-threatening experience (immediate risk of dying) ; persistent or significant disability/incapacity; congenital anomaly. Safety analysis set for Part B included all subjects who received any amount of the investigational drug (CAZ-AVI) in the Part B.

End point type	Primary

End point timeframe:

Day 1 up to maximum of Day 35 after the last dose of CAZ-AVI

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	8	
Units: Subjects				
AE's	4	4	7	
SAE's	1	2	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects who Died: Part B

End point title	Number of Subjects who Died: Part B[9][10]

End point description:

Safety analysis set for Part B included all subjects who received any amount of the investigational drug (CAZ-AVI) in the Part B.

End point type	Primary

End point timeframe:

Day 1 up to maximum of Day 35 after the last dose of CAZ-AVI

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	8	
Units: Subjects	0	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects who Discontinued Treatment and Study due to AEs: Part B

End point title	Number of Subjects who Discontinued Treatment and Study due to AEs: Part B[11][12]

End point description:

It is defined as number of subjects who permanent or temporary discontinued study medication due to any AE, treatment related AEs were reported. The risk period (RP) was the minimum of last contact date or last study treatment dose date + 28 days. The last contact date was the maximum of (AE start date, AE stop date, last study visit date, withdrawal date, telephone contact date). Safety analysis set for Part B included all subjects who received any amount of the investigational drug (CAZ-AVI) in the Part B.

End point type	Primary

End point timeframe:

Day 1 up to 35 days after the last dose of study drug (CAZ-AVI)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	8	
Units: Subjects				
Discontinued treatment due to AEs	0	0	2	
Discontinued treatment due to AE & continued study	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Laboratory Parameters Occurred in More than 2 Subjects: Part B

End point title	Number of Subjects With Clinically Significant Laboratory Parameters Occurred in More than 2 Subjects: Part B[13][14]

End point description:

Number of subjects in Part B with clinically significant abnormal laboratory parameters that occurred in more than 2 subjects from Day 1 up to 35 days after the last dose of CAZ-AVI were reported in this endpoint. Clinically significant labs were abnormal laboratory results which the investigator reported as being clinically significant. Safety analysis set for Part B included all subjects who received any amount of the investigational drug (CAZ-AVI) in the Part B.

End point type	Primary

End point timeframe:

Day 1 up to a maximum of 35 days after the last dose of CAZ-AVI

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	8	
Units: Subjects				
Hematology: Hematocrit	2	0	1	
Hematology: Hemoglobin	2	0	2	
Hematology: Leukocytes	0	2	1	

Hematology: Neutrophils/Leukocytes	1	2	0	
Hematology: Platelets	1	1	2	
Clinical Chemistry:Alanine Aminotransferase	1	1	1	
Clinical Chemistry: Albumin	1	2	2	
Clinical Chemistry: Aspartate Aminotransferase	1	2	1	
Clinical Chemistry: Base Excess	0	3	3	
Clinical Chemistry: Bilirubin	0	1	2	
Clinical Chemistry: Blood PH	0	3	3	
Clinical Chemistry: C Reactive Protein	2	4	8	
Clinical Chemistry: Direct Bilirubin	0	1	3	
Clinical Chemistry:Partial Pressure Carbon Dioxide	0	1	2	
Clinical Chemistry: Potassium	0	2	1	
Clinical Chemistry: Procalcitonin	0	2	4	
Urinalysis	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs): Part A

End point title	Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs): Part A[15]

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent AEs were events between first dose of study drug and up to late follow-up (LFU) visit (28 to 35 days after last dose of study treatment [IV or oral]) that were absent before treatment or that worsened relative to pretreatment state. Safety analysis set for Part A included all subjects who received any amount of the investigational drug (CAZ-AVI) in the Part A.

End point type	Secondary

End point timeframe:

Day 1 up to maximum of Day 35 after the last dose of CAZ-AVI

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part A: Cohort 1	Part A: Cohort 2	Part A: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	8	
Units: Subjects				
AE's	4	2	2	
SAE's	2	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Died: Part A

End point title	Number of Subjects who Died: Part A[16]

End point description:

Safety analysis set for Part A included all subjects who received any amount of the investigational drug (CAZ-AVI) in the Part A.

End point type	Secondary

End point timeframe:

Day 1 up to 35 days after the last dose of study drug (CAZ-AVI)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part A: Cohort 1	Part A: Cohort 2	Part A: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	8	
Units: Participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Discontinued Treatment and Study due to AEs: Part A

End point title	Number of Subjects who Discontinued Treatment and Study due to AEs: Part A[17]

End point description:

It is defined as number of subjects who permanent or temporary discontinued study medication due to any AE, treatment related AEs were reported. The risk period (RP) was the minimum of last contact date or last study treatment dose date + 28 days. The last contact date was the maximum of (AE start date, AE stop date, last study visit date, withdrawal date, telephone contact date). Safety analysis set for Part A included all subjects who received any amount of the investigational drug (CAZ-AVI) in the Part A.

End point type	Secondary

End point timeframe:

Day 1 up to 35 days after the last dose of study drug (CAZ-AVI)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part A: Cohort 1	Part A: Cohort 2	Part A: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	8	
Units: Subjects				
Discontinued treatment due to AEs	0	0	0	
Discontinued study due to AEs and continue study	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Ceftazidime and Avibactam 2 Hours, 2 Hours and 30 Minutes, 7 Hours Post Doses: Part B

End point title	Plasma Concentrations of Ceftazidime and Avibactam 2 Hours, 2 Hours and 30 Minutes, 7 Hours Post Doses: Part B[18]

End point description:

The Pharmacokinetic (PK) analysis set for Part B is defined as participants who received a single IV dose of CAZ-AVI in Part B. Each Cohort 1, 2, and 3, the plasma concentration will be summarized by nominal sampling time using appropriate descriptive such as Mean and standard deviation.

End point type	Secondary

End point timeframe:

2 hours, 2 hours 30 mins, and 3 hours post-dose on Day 1

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	8	
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
Ceftazidime: 2 hours	52950.0 (± 17565.47)	48625.0 (± 17010.46)	43711.3 (± 22229.93)	
Ceftazidime: 2 hours 30 mins	43037.5 (± 17433.21)	39000.0 (± 4415.88)	42465.0 (± 26800.19)	
Ceftazidime: 7 hours	8323.8 (± 4805.65)	16735.0 (± 9070.87)	18658.4 (± 18268.92)	
Avibactam: 2 hours	10340.0 (± 3262.63)	11330.0 (± 2012.53)	9410.1 (± 5551.00)	
Avibactam: 2 hours 30 mins	6825.0 (± 2386.26)	9380.0 (± 2317.14)	9064.0 (± 5694.05)	
Avibactam: 7 hours	1025.3 (± 592.83)	3787.5 (± 2533.46)	3890.5 (± 3867.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Laboratory Parameters Occurred in More than 2 Subjects: Part A

End point title	Number of Subjects With Clinically Significant Laboratory Parameters Occurred in More than 2 Subjects: Part A[19]

End point description:

Number of subjects in Part A with clinically significant abnormal laboratory parameters that occurred in more than 2 subjects from Day 1 up to 35 days after the last dose of CAZ-AVI were reported in this endpoint. Clinically significant labs were abnormal laboratory results which the investigator reported as being clinically significant. Safety analysis set for Part A included all subjects who received any amount of the investigational drug (CAZ-AVI) in the Part A.

End point type	Secondary

End point timeframe:

Day 1 up to 35 days after the last dose of CAZ-AVI

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part A: Cohort 1	Part A: Cohort 2	Part A: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	8	
Units: Subjects				
Hematology: Hematocrit	1	1	2	
Hematology: Hemoglobin	1	1	2	
Hematology: Leukocytes	1	2	3	
Blood chemistry	0	0	0	
Urinalysis	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects According to Clinical Outcome After End of IV Treatment(EOIV), End of Treatment(EOT), Test of Cure(TOC) and Late Follow-Up(LFU): Intent to Treat Analysis Population: Part B

End point title	Number of Subjects According to Clinical Outcome After End of IV Treatment(EOIV), End of Treatment(EOT), Test of Cure(TOC) and Late Follow-Up(LFU): Intent to Treat Analysis Population: Part B[20]

End point description:

Clinical outcomes will be summarized descriptively for all efficacy analysis sets from Part B:Intent-to-Treat Population For each nominal timepoint (End of IV, End of Treatment, Test of Cure, and Late Follow-Up). Clinical outcome was defined as when subject experienced clinical cure or clinical improvement. Clinical cure=resolution of all acute signs and symptoms of infection or improvement to such an extent that no further antibacterial therapy was required. Clinical improvement= subjects who switched to oral therapy and met the following criteria at EOIV: febrile (temperature less than or equal to 38.0 deg C) for at least 24 hours. Absence of new and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from baseline and worsening of none.

End point type	Secondary

End point timeframe:

EOIV, EOT, TOC, LFU

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	8	
Units: Subjects				
EOIV: Clinical cure	2	2	3	
EOIV: Clinical improvement	6	2	3	
EOIV: Clinical failure	0	0	1	
EOIV: Indeterminate	0	1	1	
EOIV: Missing	0	0	0	
EOT: Clinical cure	6	3	3	
EOT: Clinical improvement	2	1	3	
EOT: Clinical failure	0	0	1	
EOT: Indeterminate	0	1	0	
EOT: Missing	0	0	1	
LFU: Clinical cure	8	4	6	
LFU: Clinical improvement	0	0	0	
LFU: Clinical failure	0	0	1	
LFU: Indeterminate	0	1	0	
LFU: Missing	0	0	0	
TOC: Clinical cure	7	3	7	
TOC: Clinical improvement	0	0	0	
TOC: Clinical failure	0	0	1	
TOC: Indeterminate	0	2	0	
TOC: Missing	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects According to Clinical Outcome After End of IV Treatment(EOIV), End of Treatment(EOT), Test of Cure(TOC) and Late Follow-Up(LFU) in Micro-ITT Analysis Population: Part B

End point title	Number of Subjects According to Clinical Outcome After End of IV Treatment(EOIV), End of Treatment(EOT), Test of Cure(TOC) and Late Follow-Up(LFU) in Micro-ITT Analysis Population: Part B[21]

End point description:

Clinical outcomes will be summarized descriptively for all efficacy analysis sets from Part B:Micro ITT Population. For each nominal timepoint (End of IV, End of Treatment, Test of Cure, and Late Follow-Up). Clinical outcome was defined as when subject experienced clinical cure or clinical improvement. Clinical cure=resolution of all acute signs and symptoms of infection or improvement to such an extent that no further antibacterial therapy was required. Clinical improvement= subjects who switched to oral therapy and met the following criteria at EOIV: febrile (temperature less than or equal to 38.0 deg C) for at least 24 hours. Absence of new and improvement in at least 1 symptom or sign (ie, fever, pain,

tenderness, elevated WBCs, elevated CRP) from baseline and worsening of none. Microbiological Intent-to-Treat (micro ITT) set was defined as subjects who received at least 1 Gram-negative pathogen in an adequate initial/prestudy culture.

End point type	Secondary

End point timeframe:

EOIV, EOT, TOC, LFU

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	0[22]	3	
Units: Subjects				
EOIV: Clinical cure	2		1	
EOIV: Clinical improvement	5		0	
EOIV: Clinical failure	0		1	
EOIV: Indeterminate	0		1	
EOIV: Missing	0		0	
EOT: Clinical cure	6		1	
EOT: Clinical improvement	1		0	
EOT: Clinical failure	0		1	
EOT: Indeterminate	0		0	
EOT: Missing	0		1	
LFU: Clinical cure	7		1	
LFU: Clinical improvement	0		0	
LFU: Clinical failure	0		1	
LFU: Indeterminate	0		0	
LFU: Missing	0		0	
TOC: Clinical cure	6		2	
TOC: Clinical improvement	0		0	
TOC: Clinical failure	0		1	
TOC: Indeterminate	0		0	
TOC: Missing	0		0	

Notes:

[22] - No subjects were analysed for this reporting group in this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects According to Clinical Outcome After End of IV Treatment(EOIV), End of Treatment(EOT), Test of Cure(TOC) and Late Follow-Up(LFU) in Modified-ITT Analysis Population: Part B

End point title	Number of Subjects According to Clinical Outcome After End of IV Treatment(EOIV), End of Treatment(EOT), Test of Cure(TOC) and Late Follow-Up(LFU) in Modified-ITT Analysis Population: Part B[23]

End point description:

Clinical outcomes summarized for all efficacy analysis sets from Part B:Modified ITT population at EOIV, EOT, TOC, LFU. Clinical outcome=clinical cure or improvement. Clinical cure=resolution of all acute signs

and symptoms of infection or improvement; no further antibacterial therapy was required. Clinical improvement= subjects who switched to oral therapy and met following criteria at EOIV: febrile (temperature less than or equal to 38.0 deg C) for at least 24 hours. Absence of new and improvement in at least 1 symptom or sign (fever, pain, tenderness, elevated WBCs, elevated CRP) from baseline and worsening of none. Modified ITT set=subjects who received at least 1 Gram-negative pathogen in an adequate initial/prestudy culture. Received CAZ-AVI, met minimal disease criteria of infection(presence of at least 1 clinical criterion,1 laboratory criterion or met at least 2 clinical criteria in presence of, or result of suspected or proven bacterial infection required IV antibiotic).

End point type	Secondary

End point timeframe:

EOIV, EOT, TOC, LFU

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	5	
Units: Subjects				
EOIV: Clinical cure	2	1	3	
EOIV: Clinical improvement	6	1	0	
EOIV: Clinical failure	0	0	1	
EOIV: Indeterminate	0	1	1	
EOIV: Missing	0	0	0	
EOT: Clinical cure	6	1	3	
EOT: Clinical improvement	2	1	0	
EOT: Clinical failure	0	0	1	
EOT: Indeterminate	0	1	0	
EOT: Missing	0	0	1	
LFU: Clinical cure	8	2	3	
LFU: Clinical improvement	0	0	0	
LFU: Clinical failure	0	0	1	
LFU: Indeterminate	0	1	0	
LFU: Missing	0	0	0	
TOC: Clinical cure	7	1	4	
TOC: Clinical improvement	0	0	0	
TOC: Clinical failure	0	0	1	
TOC: Indeterminate	0	2	0	
TOC: Missing	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects According to Microbiological Response at TOC Visit in Micro-ITT population: Part B

End point title	Number of Subjects According to Microbiological Response at TOC Visit in Micro-ITT population: Part B[24]

End point description:

The per-pathogen microbiological outcome categories at TOC were defined as responses of eradication, presumed eradication, persistence, presumed persistence and indeterminate. Eradication was defined as source specimen demonstrated absence of the original baseline pathogen. Presumed eradication was defined as source specimen was not available to culture and the subject was assessed as a clinical cure. Persistence was defined as source specimen demonstrates continued presence of the original baseline pathogen. Presumed persistence was defined as source specimen was not available to culture and the subject was assessed as a clinical failure. Indeterminate was defined as source specimen was not available to culture and the subject's clinical outcome was assessed as indeterminate. Microbiological Intent-to-Treat (micro ITT) set was defined as subjects who received at least 1 Gram-negative pathogen in an adequate initial/prestudy culture.

End point type	Secondary

End point timeframe:

TOC

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	0[25]	3	
Units: Subjects				
Enterobacter Cloacae Complex: F: Eradication	0		0	
EnterobacterCloacae Complex:F:Presumed eradication	0		0	
Enterobacter Cloacae Complex: U: Persistence	0		0	
EnterobacterCloacae Complex:U:Presumed persistence	0		1	
Enterobacter Cloacae Complex Indeterminate	0		0	
E.coli: F: Eradication	4		0	
E.coli: F: Presumed eradication	2		0	
E.coli: U: Persistence	0		0	
E.coli:U:Presumed persistence	0		0	
E.coli:Indeterminate	0		0	
Klebsiella Oxytoca:F: Eradication	0		0	
Klebsiella Oxytoca:F:Presumed eradication	0		1	
Klebsiella Oxytoca:U: Persistence	0		0	
Klebsiella Oxytoca:U:Presumed persistence	0		0	
Klebsiella Oxytoca: Indeterminate	0		0	
Klebsiella Pneumoniae:F: Eradication	0		0	
Klebsiella Pneumoniae:F:Presumed eradication	0		1	
Klebsiella Pneumoniae:U: Persistence	0		0	
Klebsiella Pneumoniae:U:Presumed persistence	0		0	
Klebsiella Pneumoniae: Indeterminate	0		0	

Notes:

[25] - No subjects were analysed for this reporting group in this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Emergent Infections in Micro-ITT Analysis Population: Part B

End point title	Number of Subjects With Emergent Infections in Micro-ITT Analysis Population: Part B[26]

End point description:

Superinfection: a culture identified pathogen other than a baseline pathogen during the course of active treatment with study therapy requiring alternative antimicrobial therapy. New infection: a culture identified pathogen other than a baseline pathogen at any time after study treatment has finished requiring alternative antimicrobial therapy. Microbiological Intent-to-Treat (micro ITT) set was defined as subjects who received at least 1 Gram-negative pathogen in an adequate initial/prestudy culture.

End point type	Secondary

End point timeframe:

Day 1 up to 35 days after the last dose of study drug (CAZ-AVI)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Part B: Cohort 1	Part B: Cohort 2	Part B: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	0[27]	3	
Units: Subjects				
Superinfection	0		0	
New infection	0		0	

Notes:

[27] - No subjects were analysed for this reporting group in this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to 35 days after the last dose of study drug (CAZ-AVI)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25

Reporting groups	
Reporting group title	Part A: Cohort 1
Reporting group description:	
On Day 1 subjects aged 28days to < 3 months old received a single IV infusion of CAZ-AVI 30 mg/kg CAZ and 7.5 mg/kg AVI over a 2-hour (+/-10 min) period.	
Reporting group title	Part A: Cohort 3
Reporting group description:	
On Day 1 subjects aged >=26 week to <37week and <=28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period.	
Reporting group title	Part B: Cohort 1
Reporting group description:	
On Day 1 subjects aged 28days to <3 months old received a single IV infusion of CAZ-AVI 30 milligrams per kilogram (mg/kg) CAZ and 7.5 mg/kg AVI over a 2-hour (+/-10 min) period every 8 hours (+/-1 hour).	
Reporting group title	Part B: Cohort 2
Reporting group description:	
On Day 1 subjects aged >= 37week and <= 28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over 2-hour (+/-10 min) period every 8 hours (+/-1 hour).	
Reporting group title	Part B: Cohort 3
Reporting group description:	
On Day 1 subjects aged >=26week to <37week and <=28days old received a single IV infusion of CAZ-AVI 20 mg/kg CAZ and 5.0 mg/kg AVI over a 2-hour (+/-10 min) period every 8 hours (+/-1 hour).	

Serious adverse events	Part A: Cohort 1	Part A: Cohort 3	Part B: Cohort 1
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)	1 / 8 (12.50%)	1 / 8 (12.50%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 8 (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
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Necrotising colitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 8 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 8 (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
Infections and infestations			
Enterococcal sepsis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			

subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter sepsis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida sepsis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Septic shock			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B: Cohort 2	Part B: Cohort 3	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	2 / 8 (25.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac failure acute			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Necrotising colitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 5 (20.00%)	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			
Oliguria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Enterococcal sepsis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Part A: Cohort 1	Part A: Cohort 3	Part B: Cohort 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	3 / 8 (37.50%)
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Skin and subcutaneous tissue disorders Decubitus ulcer subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Infections and infestations Sepsis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0

Non-serious adverse events	Part B: Cohort 2	Part B: Cohort 3	
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 5 (20.00%)	4 / 8 (50.00%)	
Investigations Oxygen saturation decreased subjects affected / exposed occurrences (all) Transaminases increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0 0 / 5 (0.00%) 0	1 / 8 (12.50%) 1 0 / 8 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	2 / 8 (25.00%) 2	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 8 (12.50%) 1	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 8 (12.50%) 1	

Skin and subcutaneous tissue disorders Decubitus ulcer subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0	 2 / 8 (25.00%) 2	
Infections and infestations Sepsis subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1	 2 / 8 (25.00%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2019	Primary purpose was to revise the enrollment sequence so Part B Cohort 3 would begin enrollment after data from the other cohorts was evaluated, as requested by the EMA Pediatric Committee (PDCO) on 19-Oct-2018.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 March 2020	Enrollment was paused at all sites due to COVID-19.	30 April 2020

Notes:

Limitations and caveats

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

One subject died after the study in Part B: Cohort 1 group. This number was not included in the death number as it occurred after the study (more than 35 days after the last dose of the study drug).

Notes: