Clinical trial results:
A Phase IIa Prospective, Open-Label, Multicenter Study to Determine the Pharmacokinetics (PK) and Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) for the Treatment of Complicated Intra-Abdominal Infections (cIAIs) in Hospitalized Adults

Summary

EudraCT number	2015-002726-39
Trial protocol	DE ES
Global end of trial date	26 October 2017

Results information

Result version number	v1 (current)
This version publication date	09 November 2018
First version publication date	09 November 2018

Trial information

Trial identification

Sponsor protocol code	C3601001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02655419
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: D4910C00009

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 1-800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 1-800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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	29 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the Pharmacokinetics (PK) and to access the safety of Aztreonam-Avibactam (ATM-AVI) in this subject population. To assess the safety of ATM-AVI in this patient population.

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	19 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Spain: 34
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	29
From 65 to 84 years	11

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at 11 centers in 3 countries from 19-May-2016 to 26-Oct-2017. A total of 40 subjects were screened, 4 screen failures, 36 assigned to treatment and 34 received treatment. Two subjects in ATM-AVI + Metronidazole : High AVI Dose Cohort arm did not received study drug.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort

Arm description:

Subjects with normal renal function or mild renal impairment (Creatinine clearance [CrCl] greater than[>] 50 milliliter per minute [mL/min]), received intravenous (IV) infusion of 500 milligram (mg) ATM plus 137 mg AVI over 30 minutes as loading dose, followed by maintenance infusions of 1500 mg ATM plus 410 mg AVI, over a 3 hour period every 6 hours, for a minimum of 5 days and up to maximum of 14 days. Subjects also received 1 hour IV infusion of 500 mg metronidazole, every 8 hours after first ATM-AVI maintenance infusion for a minimum of 5 days and up to maximum of 14 days. All study therapies could be discontinued (after at least 5 full days of IV therapy) at the discretion of the investigator.

Arm type	Experimental
Investigational medicinal product name	Avibactam (AVI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received loading dose of 137 mg of AVI, maintenance dose 410 mg AVI of lyophilisate for concentrate for solution for infusion by intravenous infusion.

Investigational medicinal product name	Aztreonam (ATM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received loading dose of 500 mg of ATM, maintenance dose of 1500 mg of ATM powder for solution for infusion by intravenous infusion.

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 500 mg metronidazole of solution for infusion by intravenous infusion.

Arm title	ATM-AVI + Metronidazole: High AVI Dose Cohort

Arm description:

Subjects received ATM-AVI IV infusion in following manner (1. normal renal function or mild renal impairment [CrCl >50mL/min] : 500 mg ATM plus 167 mg AVI over 30 minutes as loading dose, followed by maintenance infusions of 1500 mg ATM plus 500 mg AVI, over a 3 hour period every 6 hours; 2. moderate renal impairment [CrCl 31-50 ml/min]: 500 mg ATM plus 167 mg AVI over 30 minutes as loading dose, followed by IV extended loading infusion of 1500 mg ATM plus 500 mg AVI over 3 hour, followed by maintenance infusions of 750 mg ATM plus 250 mg AVI, over 3 hour period every 6 hours) along with 1 hour IV infusion of 500 mg metronidazole, every 8 hrs after first ATM-AVI maintenance infusion. All treatments were administered for minimum 5 days and up to maximum of 14 days. All study therapies could be discontinued (after at least 5 full days of IV therapy) at the discretion of the investigator.

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

Dosage and administration details:

Subjects with CrCl >50mL/min, received loading dose of 500 mg of ATM and maintenance dose of 1500 mg. Subjects with CrCl 31-50 ml/min received loading dose of 500 mg of ATM, maintenance dose of 1500 mg followed by maintenance infusions of 750 mg of ATM powder for solution for infusion by intravenous infusion.

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 500 mg metronidazole of solution for infusion by intravenous infusion.

Investigational medicinal product name	Avibactam (AVI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with CrCl >50mL/min, received loading dose of 167 mg and maintenance dose of 500 mg of AVI. Subjects with CrCl 31-50 ml/min received loading dose of 167 mg, maintenance dose of 500 mg followed by maintenance infusions of 250 mg of AVI lyophilisate for concentrate for solution for infusion by intravenous infusion.

Number of subjects in period 1	Aztreonam-Avibactam(ATM-AVI)+Metronidazole: Low AVI Dose	ATM-AVI + Metronidazole: High AVI Dose Cohort
Started	17	23
Treated	16	18
Completed	12	16
Not completed	5	7
Consent withdrawn by subject	4	1
Unspecified	-	1
Enrolled but not treated	1	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
All subjects who were enrolled in this study either received ATM-AVI+ Metronidazole low AVI dose cohort or ATM-AVI + Metronidazole high AVI dose cohort.	

Reporting group values	Overall Study	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	11	11	
85 years and over	0	0	
Age Continuous			
Age continuous data is provided for treated subjects only (34)			
Units: years			
arithmetic mean	51.15		
standard deviation	± 13.40	-	
Sex: Female, Male Units: Subjects			
Male	30	30	
Female	10	10	
Race/Ethnicity, Customized Units: Subjects			
White	35	35	
Other	1	1	
Unknown	3	3	
Native Hawaiian or Other Pacific Islander	1	1	

End points

End points reporting groups

Reporting group title	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort

Reporting group description:

Subjects with normal renal function or mild renal impairment (Creatinine clearance [CrCl] greater than[>] 50 milliliter per minute [mL/min]), received intravenous (IV) infusion of 500 milligram (mg) ATM plus 137 mg AVI over 30 minutes as loading dose, followed by maintenance infusions of 1500 mg ATM plus 410 mg AVI, over a 3 hour period every 6 hours, for a minimum of 5 days and up to maximum of 14 days. Subjects also received 1 hour IV infusion of 500 mg metronidazole, every 8 hours after first ATM-AVI maintenance infusion for a minimum of 5 days and up to maximum of 14 days. All study therapies could be discontinued (after at least 5 full days of IV therapy) at the discretion of the investigator.

Reporting group title	ATM-AVI + Metronidazole: High AVI Dose Cohort

Reporting group description:

Subjects received ATM-AVI IV infusion in following manner (1. normal renal function or mild renal impairment [CrCl >50mL/min] : 500 mg ATM plus 167 mg AVI over 30 minutes as loading dose, followed by maintenance infusions of 1500 mg ATM plus 500 mg AVI, over a 3 hour period every 6 hours; 2. moderate renal impairment [CrCl 31-50 ml/min]: 500 mg ATM plus 167 mg AVI over 30 minutes as loading dose, followed by IV extended loading infusion of 1500 mg ATM plus 500 mg AVI over 3 hour, followed by maintenance infusions of 750 mg ATM plus 250 mg AVI, over 3 hour period every 6 hours) along with 1 hour IV infusion of 500 mg metronidazole, every 8 hrs after first ATM-AVI maintenance infusion. All treatments were administered for minimum 5 days and up to maximum of 14 days. All study therapies could be discontinued (after at least 5 full days of IV therapy) at the discretion of the investigator.

Primary: Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 1, 0 hr

End point title	Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 1, 0 hr[1]

End point description:

All subjects were to have sparse pharmacokinetics (PK) sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above lower limit of quantification (LLOQ). LLOQ for ATM was 0.1 microgram per milliliter (mcg/ml). PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analysed signifies subjects who had observations above LLOQ and "99999" signifies standard deviation was not estimable since only 1 subject had concentration above LLOQ.

End point type	Primary

End point timeframe:

Predose (0 hr) 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[2]		
Units: mcg/mL				
geometric mean (geometric coefficient	0.1 (± 99999)	()		

of variation)

Notes:

[2] - None of the subjects had data above LLOQ, hence, data was not reported.

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 1, 0.42 hr

End point title	Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 1, 0.42 hr[3]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI.

End point type	Primary

End point timeframe:

0.42 hr 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM - AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	39.0 (± 262.0)	39.4 (± 58.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 1, 3.25 hr

End point title	Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 1, 3.25 hr[4]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had

observations above LLOQ.

End point type	Primary

End point timeframe:

3.25 hr Post dose on Day 1

Notes:

[4] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM - AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	55.7 (± 16.0)	58.5 (± 36.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 1, 5 hr

End point title	Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 1, 5 hr[5]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

5 hr 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM - AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	28.8 (± 23.9)	31.5 (± 50.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 1, 0 hr

End point title	Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 1, 0 hr[6]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 nanogram per milliliter (ng/ml). The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ and "99999" signifies standard deviation was not estimable since only 1 subject had concentration above LLOQ.

End point type	Primary

End point timeframe:

Predose (0 hr) at Day 1

Notes:

[6] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[7]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	24.9 (± 99999)	()		

Notes:

[7] - None of the subjects had data above LLOQ, hence, data was not reported.

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 1, 0.42 hr

End point title	Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 1, 0.42 hr[8]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment

available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

0.42 hr Post dose on Day 1

Notes:

[8] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	7852.6 (± 279.2)	9801.5 (± 61.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 1, 3.25 hr

End point title	Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 1, 3.25 hr[9]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

3.25 hr Post dose on Day 1

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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: ng/mL				
geometric mean (geometric coefficient	9976.5 (±	12982.7 (±		

of variation)	25.8)	49.7)

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 1, 5 hr

End point title	Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 1, 5 hr[10]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

5 hr Post dose on Day 1

Notes:

[10] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	4086.6 (± 35.3)	5549.0 (± 76.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 4, 0 hr

End point title	Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 4, 0 hr[11][12]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ. Intensive rather than sparse sampling was conducted for all subjects in low

AVI dose cohort (Cohort 1)on Day4 and hence sparse data not reported.

End point type	Primary

End point timeframe:

Predose (0 hr) at Day 4

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: No statistical 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: No statistical analysis was planned for this endpoint

End point values	ATM-AVI + Metronidazole: High AVI Dose Cohort			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	19.7 (± 29.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 4, 2.75 hr

End point title	Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 4, 2.75 hr[13][14]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4.Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ. Intensive rather than sparse sampling was conducted for all subjects in low AVI dose cohort (Cohort 1)on Day4 and hence sparse data not reported.

End point type	Primary

End point timeframe:

2.75 hr Post dose on Day 4

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: No statistical 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: No statistical analysis was planned for this endpoint

End point values	ATM-AVI + Metronidazole: High AVI Dose Cohort			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	46.4 (± 19.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 4, 5 hr

End point title	Plasma Concentration of Aztreonam (ATM): Sparse Sampling at Day 4, 5 hr[15][16]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ. Intensive rather than sparse sampling was conducted for all subjects in low AVI dose cohort (Cohort 1)on Day4 and hence sparse data not reported.

End point type	Primary

End point timeframe:

5 hr Post dose on Day 4

Notes:

[15] - 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: No statistical analysis was planned for this endpoint

[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: No statistical analysis was planned for this endpoint

End point values	ATM-AVI + Metronidazole: High AVI Dose Cohort			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	16.5 (± 37.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 4, 0 hr

End point title	Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 4, 0 hr[17][18]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ. Intensive rather than sparse sampling was conducted for all subjects in low AVI dose cohort (Cohort 1) on Day 4 and hence sparse data not reported.

End point type	Primary

End point timeframe:

Predose (0 hr) at Day 4

Notes:

[17] - 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: No statistical analysis was planned for this endpoint

[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: No statistical analysis was planned for this endpoint

End point values	ATM-AVI + Metronidazole: High AVI Dose Cohort			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	4048.8 (± 24.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 4, 2.75 hr

End point title	Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 4, 2.75 hr[19][20]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ. Intensive rather than sparse sampling was conducted for all subjects in low AVI dose cohort (Cohort 1) on Day 4 and hence sparse data not reported.

End point type	Primary

End point timeframe:

2.75 hr Post dose on Day 4

Notes:

[19] - 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: No statistical analysis was planned for this endpoint

[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: No statistical analysis was planned for this endpoint

End point values	ATM-AVI + Metronidazole: High AVI Dose Cohort			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	9073.6 (± 24.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 4, 5 hr

End point title	Plasma Concentration of Avibactam (AVI): Sparse Sampling at Day 4, 5 hr[21][22]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ. Intensive rather than sparse sampling was conducted for all subjects in low AVI dose cohort (Cohort 1) on Day 4 and hence sparse data not reported.

End point type	Primary

End point timeframe:

5 hr Post dose on Day 4

Notes:

[21] - 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: No statistical analysis was planned for this endpoint

[22] - 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: No statistical analysis was planned for this endpoint

End point values	ATM-AVI + Metronidazole: High AVI Dose Cohort			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	2745.7 (± 40.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration Aztreonam (ATM): Intensive Sampling at Day 4, 0 hr

End point title	Plasma Concentration Aztreonam (ATM): Intensive Sampling at Day 4, 0 hr[23]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

Predose (0 hr) on Day 4

Notes:

[23] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM - AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	18.3 (± 71.2)	20.3 (± 88.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration Aztreonam (ATM): Intensive Sampling at Day 4, 0.5 hr

End point title	Plasma Concentration Aztreonam (ATM): Intensive Sampling at Day 4, 0.5 hr[24]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

0.5 hr Post dose on Day 4

Notes:

[24] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	37.6 (± 194.0)	33.8 (± 46.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 1 hr

End point title	Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 1 hr[25]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

1 hr Post dose on Day 4

Notes:

[25] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	41.2 (± 53.5)	43.0 (± 44.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 2 hr

End point title	Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 2 hr[26]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

2 hr Post dose on Day 4

Notes:

[26] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	49.6 (± 42.5)	53.6 (± 44.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 3 hr

End point title	Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 3 hr[27]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

3 hr Post dose on Day 4

Notes:

[27] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	53.6 (± 72.0)	54.7 (± 42.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 3.25 hr

End point title	Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 3.25 hr[28]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

3.25 hr Post dose on Day 4

Notes:

[28] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	45.8 (± 36.7)	47.3 (± 49.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 3.5 hr

End point title	Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 3.5 hr[29]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

3.5 hr Post dose on Day 4

Notes:

[29] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	42.9 (± 37.9)	43.2 (± 52.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 3.75 hr

End point title	Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 3.75 hr[30]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

3.75 hr Post dose on Day 4

Notes:

[30] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	39.5 (± 41.8)	38.5 (± 57.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 4 hr

End point title	Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 4 hr[31]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

4 hr Post dose on Day 4

Notes:

[31] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	34.2 (± 44.2)	36.6 (± 63.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 5 hr

End point title	Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 5 hr[32]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4.Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

5 hr Post dose on Day 4

Notes:

[32] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	23.8 (± 56.1)	26.4 (± 76.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 6 hr

End point title	Plasma Concentration of Aztreonam (ATM): Intensive Sampling at Day 4, 6 hr[33]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for ATM was 0.1 mcg/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

6 hr Post dose on Day 4

Notes:

[33] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	22.2 (± 149.8)	19.0 (± 97.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 0 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 0 hr[34]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

Predose (0 hr) on Day 4

Notes:

[34] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	2516.2 (± 85.6)	3184.3 (± 137.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 0.5 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 0.5 hr[35]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

0.5 hr Post dose on Day 4

Notes:

[35] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	6374.4 (± 215.4)	7140.3 (± 69.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 1 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 1 hr[36]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

1 hr Post dose on Day 4

Notes:

[36] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	7369.8 (± 59.2)	9435.7 (± 64.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 2 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 2 hr[37]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

2 hr Post dose on Day 4

Notes:

[37] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	8885.4 (± 48.5)	11668.0 (± 59.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 3 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 3 hr[38]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

3 hr Post dose on Day 4

Notes:

[38] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	9820.4 (± 100.1)	11903.2 (± 62.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 3.25 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 3.25 hr[39]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

3.25 hr Post dose on Day 4

Notes:

[39] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	8009.9 (± 38.7)	9631.5 (± 66.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 3.5 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 3.5 hr[40]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

3.5 hr Post dose on Day 4

Notes:

[40] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	7095.8 (± 43.9)	8545.4 (± 83.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 3.75 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 3.75 hr[41]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

3.75 hr Post dose on Day 4

Notes:

[41] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	6340.3 (± 50.3)	7227.1 (± 88.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 4 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 4 hr[42]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

4 hr Post dose on Day 4

Notes:

[42] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	5258.7 (± 49.9)	6727.6 (± 94.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 5 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 5 hr[43]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

5 hr Post dose on Day 4

Notes:

[43] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	3300.0 (± 59.7)	4300.3 (± 120.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 6 hr

End point title	Plasma Concentration of Avibactam (AVI): Intensive Sampling at Day 4, 6 hr[44]

End point description:

All subjects were to have sparse PK sampling on Day 1; the first sequentially enrolled 25 subjects in study were to have intensive PK sampling on Day 4 while the remaining subjects were to have sparse sampling on Day 4. Data was summarized only for observations above LLOQ. LLOQ for AVI was 10 ng/ml. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies subjects who had observations above LLOQ.

End point type	Primary

End point timeframe:

6 hr Post dose on Day 4

Notes:

[44] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	3275.7 (± 205.4)	2879.2 (± 140.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Plasma Concentration (Cmax) of Aztreonam (ATM): Intensive Sampling at Day 4

End point title	Maximum Observed Plasma Concentration (Cmax) of Aztreonam (ATM): Intensive Sampling at Day 4[45]

End point description:

The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[45] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	62.5 (± 146.9)	55.4 (± 42.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Plasma Concentration (Cmax) of Avibactam (AVI): Intensive Sampling at Day 4

End point title	Maximum Observed Plasma Concentration (Cmax) of Avibactam (AVI): Intensive Sampling at Day 4[46]

End point description:

The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[46] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	11552.4 (± 164.5)	12116.2 (± 61.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Time of Observed Maximum Concentration (tmax) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4

End point title	Time of Observed Maximum Concentration (tmax) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at

	Day 4[47]

End point description:

The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[47] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM - AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: hours				
median (full range (min-max))				
ATM	2.9 (0.5 to 3.5)	2.4 (2.0 to 3.0)		
AVI	2.9 (0.5 to 3.8)	2.8 (2.0 to 3.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) for Aztreonam (ATM): Intensive Sampling at Day 4

End point title	Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) for Aztreonam (ATM): Intensive Sampling at Day 4[48]

End point description:

AUC(0-6) was defined as the area under the plasma concentration-time curve from time zero up to the six hours postdose. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[48] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: hour*microgram/milliliter (hr*mcg/mL)				
geometric mean (geometric coefficient of variation)	235.2 (± 60.6)	234.7 (± 54.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) for Avibactam (AVI): Intensive Sampling at Day 4

End point title	Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) for Avibactam (AVI): Intensive Sampling at Day 4[49]

End point description:

AUC(0-6) was defined as the area under the plasma concentration-time curve from time zero up to the six hours postdose. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[49] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: hour*nanogram per milliliter (hr*ng/mL)				
geometric mean (geometric coefficient of variation)	40437.0 (± 74.0)	47477.5 (± 79.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration Time Curve From Time Zero up to the

Last Measured Concentration (AUC[0-last]) for Aztreonam (ATM): Intensive Sampling at Day 4

End point title	Area Under the Plasma Concentration Time Curve From Time Zero up to the Last Measured Concentration (AUC[0-last]) for Aztreonam (ATM): Intensive Sampling at Day 4[50]

End point description:

AUC(0-last) was defined as the area under the plasma concentration-time curve from time zero up to the time of the last measurable concentration. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[50] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: hr*mcg/mL				
geometric mean (geometric coefficient of variation)	235.9 (± 60.4)	234.3 (± 54.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration Time Curve From Time Zero up to the Last Measured Concentration (AUC[0-last]) for Avibactam (AVI): Intensive Sampling at Day 4

End point title	Area Under the Plasma Concentration Time Curve From Time Zero up to the Last Measured Concentration (AUC[0-last]) for Avibactam (AVI): Intensive Sampling at Day 4[51]

End point description:

AUC(0-last) was defined as the area under the plasma concentration-time curve from time zero up to the time of the last measurable concentration. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[51] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	40539.5 (± 73.8)	47422.2 (± 79.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Time of Last Measured Concentration (tlast) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4

End point title	Time of Last Measured Concentration (tlast) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4[52]

End point description:

The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[52] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: hours				
median (full range (min-max))				
ATM	6.0 (6.0 to 6.5)	6.0 (5.9 to 6.0)		
AVI	6.0 (6.0 to 6.5)	6.0 (5.9 to 6.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Elimination Half-life (t1/2) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4

End point title	Plasma Elimination Half-life (t1/2) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4[53]

End point description:

Plasma elimination half-life was defined as time measured for the plasma concentration of ATM and AVI to decrease by one half of its initial concentration. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[53] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM - AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: hours				
arithmetic mean (standard deviation)				
ATM|	2.3 (± 1.06)	2.8 (± 2.05)		
AVI|	1.8 (± 0.59)	2.2 (± 1.85)		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Volume of Distribution at Steady State (Vss) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4

End point title	Apparent Volume of Distribution at Steady State (Vss) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4[54]

End point description:

Apparent volume of distribution at steady state was defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[54] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: liter				
geometric mean (geometric coefficient of variation)				
ATM	20.3 (± 16.9)	19.6 (± 31.8)		
AVI	26.0 (± 22.0)	23.7 (± 29.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Volume of Distribution (Vz) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4

End point title	Volume of Distribution (Vz) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4[55]

End point description:

Apparent volume of distribution was defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[55] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: liter				
geometric mean (geometric coefficient of variation)				
ATM	21.4 (± 15.3)	21.6 (± 24.1)		
AVI	28.2 (± 20.4)	27.4 (± 20.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Clearance (CL) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4

End point title	Apparent Clearance (CL) of Aztreonam (ATM) and Avibactam (AVI): Intensive Sampling at Day 4[56]

End point description:

Clearance of a drug was measure of the rate at which a drug was metabolized or eliminated by normal biological processes. The PK population included all subjects who had at least 1 plasma concentration data assessment available for ATM-AVI. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4

Notes:

[56] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM - AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: liter/hour				
geometric mean (geometric coefficient of variation)				
ATM	6.4 (± 35.4)	6.4 (± 35.5)		
AVI	10.1 (± 42.6)	10.5 (± 41.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[57]

End point description:

An AE was any untoward medical occurrence in a subject who received investigational product without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; or was an important medical event which may jeopardise the subjec or require medical intervention to prevent one of the above outcomes. Treatment-emergent AEs were events occurring between first infusion of study drug and up to late follow-up (LFU) visit (up to Study Day 38). AEs included both non-serious AEs and SAEs. The safety analysis included all enrolled subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug up to the LFU visit (up to maximum of 38 days)

Notes:

[57] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: subjects				
AEs|	11	12		
SAEs|	4	5		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects With Electrocardiogram (ECG) Abnormalities[58]

End point description:

Criteria for ECG abnormalities: QT value: greater than or equal to (>=) 450 milliseconds (msec), >=480 msec, >=500 msec, >=500 msec and increase from baseline >=60 msec. Increase from baseline in QT: >=30 msec, >=60 msec. Decrease from baseline in QT: >=30 msec, >=60 msec. QTcB value: >=450 msec, >=480 msec, >=500 msec, >=500 and increase from baseline >=60 msec. Increase from baseline in QT interval using Bazett's correction (QTcB) value: >=30 msec, >=60 msec. Decrease from baseline in QTcB: >=30 msec, >=60 msec. QT interval using Fridericia's correction (QTcF) value: >=450 msec, >=480 msec, >=500 msec, >=500 msec and increase from baseline >=60 msec. Increase from baseline in QTcF value: >=30 msec, >=60 msec. Decrease from baseline in QTcF value: >=30 msec, >=60 msec. EOT (end of treatment) visit occurred within 24 hours after last infusion. The safety analysis included all enrolled subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

Baseline up to EOT (up to maximum treatment duration of 15 days)

Notes:

[58] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: subjects				
QT value >=450	2	0		
QT value >=480	2	0		
QT value >=500	2	0		

QT value >=500 and increase from baseline >=60	1	0		
Increase in QT >=30	6	4		
Increase in QT>=60	2	1		
Decrease in QT >=30	1	1		
Decrease in QT>=60	0	1		
QTcB value >=450	5	1		
QTcB value >=480	2	0		
QTcB value >=500	1	0		
QTcB value >=500 and increase from baseline >=60	0	0		
Increase in QTcB >=30	3	1		
Increase in QTcB >=60	0	1		
Decrease in QTcB >=30	2	1		
Decrease in QTcB >=60	0	0		
QTcF value >=450	4	0		
QTcF value >=480	2	0		
QTcF value >=500	1	0		
QTcF value >=500 and increase from baseline >=60	0	0		
Increase in QTcF >=30	3	2		
Increase in QTcF >=60	0	0		
Decrease in QTcF >=30	0	1		
Decrease in QTcF >=60	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities in Hematology Parameters

End point title	Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities in Hematology Parameters[59]

End point description:

Criteria for abnormality: hemoglobin, hematocrit, erythrocytes less than(<) 0.7*lower limit of normal [LLN] and (&) greater than (>) 30 percent (%) below baseline [BB]; >1.3*upper limit of normal [ULN] & >30% above baseline [AB], leukocytes <0.65*LLN & >60% BB; >1.6* ULN & >100% AB; platelets <0.65*LLN & >50% BB; >1.5*ULN & >100% AB; neutrophils <0.65*LLN & >75% BB; >1.6*ULN & >100% AB, lymphocytes <0.25*LLN & >75%BB; >1.5*ULN & >100% AB, basophils, eosinophils, monocytes>4.0*ULN & >300% AB. LFU visit occurred within 20 to 24 days after last infusion. The safety analysis included all enrolled subjects who received any amount of study drug. Here, Overall number of subjects analysed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to LFU visit (up to maximum of 38 days)

Notes:

[59] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	17		
Units: subjects				
Hemoglobin: <0.7*LLN&>30% BB	0	0		
Hemoglobin: >1.3*ULN&>30% AB	0	0		
Hematocrit: <0.7*LLN&>30% BB	0	0		
Hematocrit:>1.3*ULN&>30% AB	0	0		
Erythrocytes:<0.7*LLN&>30% BB	0	0		
Erythrocytes: >1.3*ULN&>30% AB	0	0		
Leukocytes: <0.65*LLN&>60%BB	0	0		
Leukocytes:>1.6* ULN&>100%AB	1	0		
Platelets: <0.65*LLN&>50%BB	0	0		
Platelets: >1.5*ULN&>100% AB	1	5		
Neutrophils:<0.65*LLN&>75% BB	0	0		
Neutrophils: >1.6*ULN & >100% AB	1	1		
Lymphocytes: <0.25*LLN&>75%BB	0	0		
Lymphocytes: >1.5*ULN&>100%AB	0	0		
Basophils: >4.0*ULN&>300% AB	0	0		
Eosinophils: >4.0*ULN&>300% AB	0	0		
Monocytes: >4.0*ULN&>300% AB	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities in Clinical Chemistry Parameters

End point title	Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities in Clinical Chemistry Parameters[60]

End point description:

Criteria for abnormality: aspartate aminotransferase, alanine aminotransferase >3.0*ULN&>100% AB, alkaline phosphatase <0.5 *LLN&>80% BB&; >3.0*ULN & >100% AB; bilirubin >1.5*ULN & >100% AB; direct bilirubin >2.0*ULN & >150% AB; protein <0.5*LLN & >50%BB; >1.5*ULN & >50% AB, albumin <0.5*LLN & >50% BB; >1.5*ULN & >50% AB, urea nitrogen <0.2* LLN & >100% BB; >3.0*ULN & >200% AB, creatinine >2.0*ULN & >100% AB, sodium <0.85*LLN & >10% BB;>1.1*ULN &>10% AB; potassium <0.8*LLN &>20% BB; >1.2*ULN &>20% AB, chloride <0.8*LLN &>20% BB;>1.2*ULN & >20% AB, calcium <0.7*LLN & >30% BB; >1.3*ULN & >30% AB, phosphate <0.5*LLN & >50% BB; >3.0*ULN & >200% AB, bicarbonate <0.7*LLN & >40% BB; >1.3*ULN & >40% AB, glucose <0.6*LLN & >40% BB, >3.0*ULN & >200% AB. LFU visit occurred within 20 to 24 days after last infusion. Safety analysis: all enrolled subjects who received any amount of study drug. Here, Overall number of subjects analysed signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to LFU visit (up to maximum of 38 days)

Notes:

[60] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	17		
Units: subjects				
Aspartate aminotransferase: >3.0*ULN&>100% AB	1	0		
Alanine aminotransferase:>3.0x ULN	2	2		
Alkaline phosphatase: <0.5 *LLN&>80% BB&	0	0		
Alkaline phosphatase:>3.0*ULN&>100%AB	0	0		
Bilirubin: >1.5*ULN&>100%AB	0	0		
Direct Bilirubin : >2.0*ULN&>150% AB	0	0		
Protein: <0.5*LLN &>50%BB	0	0		
Protein: >1.5*ULN&>50% AB	0	0		
Albumin: <0.5*LLN&>50%BB	0	0		
Albumin: >1.5*ULN&>50%AB	0	0		
Urea nitrogen: <0.2* LLN&>100%BB	0	0		
Urea nitrogen: >3.0*ULN&>200%AB	0	0		
Creatinine: >2.0*ULN&>100%AB	0	0		
Sodium: < 0.85*LLN&>10%BB	0	0		
Sodium: >1.1*ULN&>10%AB	0	0		
Potassium: <0.8*LLN&>20%BB	1	1		
Potassium: >1.2*ULN&>20%AB	0	0		
Chloride: <0.8*LLN&>20%BB	0	0		
Chloride: >1.2*ULN&>20%AB	0	0		
Calcium: <0.7*LLN&>30% BB	0	0		
Calcium: >1.3*ULN&>30%AB	0	0		
Phosphate: <0.5*LLN&>50% BB	0	0		
Phosphate: >3.0*ULN&>200% AB	0	0		
Bicarbonate: <0.7*LLN&>40% BB	0	0		
Bicarbonate: >1.3*ULN&>40%AB	0	0		
Glucose: <0.6*LLN&>40% BB	0	0		
Glucose: >3.0*ULN&>200%AB	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Vital Signs

End point title	Number of Subjects With Clinically Significant Vital Signs[61]

End point description:

Vital sign parameters included: Supine systolic blood pressure (millimeters of mercury [mmHg]), Supine diastolic blood pressure (mmHg), Heart rate (beats per min), Respiratory rate (breaths per min) and body temperature (degree celsius). Criteria for clinical significance in vital signs was based on investigator's assessment. LFU visit occured within 20 to 24 days after last infusion. The safety analysis included all enrolled subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug up to LFU visit (up to maximum of 38 days)

Notes:

[61] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: subjects				
Supine systolic blood pressure	0	0		
Supine diastolic blood pressure	0	0		
Heart rate	0	0		
Respiratory rate	0	1		
Temperature	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinical Significant Physical Examination Findings : MITT Population

End point title	Number of Subjects With Clinical Significant Physical Examination Findings : MITT Population[62]

End point description:

Physical examinations included an assessment of abdomen, cardiovascular, general appearance, head, eyes, ears, nose, lymph nodes, skin, musculoskeletal, neurological, respiratory systems other (edemas). Clinically significant abnormality in physical examination was based on investigator's assessment. LFU visit occured within 20 to 24 days after last infusion. The MITT population included all enrolled subjects who received any amount of study drug. Here, 'number analysed ' = subjects evaluable for this endpoint at specified categories.

End point type	Primary

End point timeframe:

From first dose of study drug up to the LFU visit (up to maximum of 38 days)

Notes:

[62] - 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: No statistical analysis was planned for this endpoint

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: subjects				
Abdomen (n= 13, 17)	1	0		

Cardiovascular (n= 13, 17)	0	0		
General appearance (n= 13, 17)	0	1		
Head, Eyes, Ears, Nose (n= 13, 17)	0	0		
Lymph nodes (n= 13, 17)	0	0		
Musculoskeletal system (n= 13, 17)	0	0		
Neurological system (n= 13, 17)	0	0		
Other (n=3, 2)	0	1		
Respiratory system (n= 13, 17)	0	1		
Skin (n= 13, 17)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Cure at Test of Cure (TOC) Visit: MITT Population

End point title	Percentage of Subjects With Clinical Cure at Test of Cure (TOC) Visit: MITT Population

End point description:

Clinical cure was defined as complete resolution or significant improvement of signs and symptoms of the index infection (cIAI) such as no further antimicrobial therapy, drainage, or surgical intervention is necessary and does not meet any of the failure criteria. Failure: death related to intra-abdominal infection; received treatment with additional antibiotics for ongoing symptoms of cIAI; previously met criteria for failure; persisting or recurrent infection within the abdomen; post-surgical wound infections included an open wound with signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or non-routine wound care. TOC visit occurred up to a maximum of 28 days after first dose. The MITT population included all enrolled subjects who received any amount of study drug.

End point type	Secondary

End point timeframe:

Test of Cure Visit (up to a maximum of 28 days)

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: percentage of subjects				
number (confidence interval 95%)	62.5 (35.4 to 84.8)	55.6 (30.8 to 78.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Cure at TOC Visit: Microbiologically Modified Intent-to-Treat (mMITT) Population

End point title	Percentage of Subjects With Clinical Cure at TOC Visit: Microbiologically Modified Intent-to-Treat (mMITT) Population

End point description:

Clinical cure defined as complete resolution or significant improvement of signs and symptoms of index infection(cIAI)such as no further antimicrobial therapy, drainage, or surgical intervention necessary and does not meet any of failure criteria. Failure:death related to intra-abdominal infection; received treatment with additional antibiotics for ongoing symptoms of cIAI; previously met criteria for failure; persisting or recurrent infection within abdomen; post-surgical wound infections included open wound with signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or non-routine wound care. TOC visit occurred up to a maximum of 28 days after first dose. mMITT population:all enrolled subjects who had any amount of study drug, diagnosis of cIAI(that met inclusion criterion)and intraabdominal pathogen at baseline. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Test of Cure Visit (up to a maximum of 28 days)

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: percentage of subjects				
number (confidence interval 95%)	66.7 (34.9 to 90.1)	54.5 (23.4 to 83.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) of Aztreonam (ATM) for Subjects With Clinical Cure and Failure at TOC Visit: Intensive Sampling at Day 4 (MITT Population)

End point title	Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) of Aztreonam (ATM) for Subjects With Clinical Cure and Failure at TOC Visit: Intensive Sampling at Day 4 (MITT Population)

End point description:

AUC(0-6):area under plasma concentration-time curve from time 0upto 6hrs. Clinical cure:complete resolution/significant improvement signs&symptoms of index infection(cIAI) i.e no antimicrobial therapy,drainage/surgical intervention necessary&doesn’t meet failure criteria. Failure:death related to intraabdominal infection; received treatment with additional antibiotics for ongoing symptoms of cIAI; previously met criteria for failure; persisting/recurrent infection within abdomen; postsurgical wound infections included open wound with signs local infection i.e purulent exudates,erythema/warmth requires additional antibiotics &/or nonroutine wound care. Data of AUC(0-6)based on intensive sampling at Day4, is reported in this endpoint separately&only for those subjects who had clinical response of cure&failure at TOC visit.TOC visit occurred upto a maximum of 28 days after first dose.MITTpopulation set used.‘n’ =subjects evaluable for this endpoint at specified categories.

End point type	Secondary

End point timeframe:

Plasma samples collection for AUC0-6 at: predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4 assessed for subjects with cure and failure at Test of Cure Visit (up to a maximum of 28 days)

End point values	Aztreonam-Avibactam(ATM - AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: hr*mcg/mL				
geometric mean (geometric coefficient of variation)				
Clinical Cure (n = 10, 4)	226.0 (± 43.0)	218.7 (± 28.5)		
Clinical Failure (n = 3, 2)	268.9 (± 88.3)	169.8 (± 14.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) of Avibactam (AVI) for Subjects With Clinical Cure and Failure at TOC Visit: Intensive Sampling at Day 4 (MITT Population)

End point title	Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) of Avibactam (AVI) for Subjects With Clinical Cure and Failure at TOC Visit: Intensive Sampling at Day 4 (MITT Population)

End point description:

AUC(0-6):area under plasma concentration-time curve from time 0upto 6hrs. Clinical cure:complete resolution/significant improvement signs&symptoms of index infection(cIAI) i.e no antimicrobial therapy,drainage/surgical intervention necessary&doesn’t meet failure criteria. Failure:death related to intraabdominal infection; received treatment with additional antibiotics for ongoing symptoms of cIAI; previously met criteria for failure; persisting/recurrent infection within abdomen; postsurgical wound infections included open wound with signs local infection i.e purulent exudates,erythema/warmth requires additional antibiotics &/or nonroutine wound care. Data of AUC(0-6)based on intensive sampling at Day4, is reported in this endpoint separately&only for those subjects who had clinical response of cure&failure at TOC visit.TOCvisit occurred up to a maximum of 28 days after first dose.MITTpopulation set used.‘n’ =subjects evaluable for this endpoint at specified categories.

End point type	Secondary

End point timeframe:

Plasma samples collection for AUC0-6 at: predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4 assessed for subjects with cure and failure at Test of Cure Visit (up to a maximum of 28 days)

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
Clinical Cure (n = 10, 4)	38003.8 (± 45.7)	40314.0 (± 36.1)		
Clinical Failure (n = 3, 2)	49730.0 (± 100.1)	34633.7 (± 10.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) of Aztreonam (ATM) for Subjects With Clinical Cure and Failure at TOC Visit: Intensive Sampling at Day 4 (mMITT Population)

End point title	Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) of Aztreonam (ATM) for Subjects With Clinical Cure and Failure at TOC Visit: Intensive Sampling at Day 4 (mMITT Population)

End point description:

AUC(0-6):area under plasma concentration-time curve from time 0upto 6hrs. Clinical cure:complete resolution/significant improvement signs&symptoms of index infection(cIAI) i.e no antimicrobial therapy,drainage/surgical intervention necessary&doesn’t meet failure criteria. Failure:death related to intraabdominal infection; received treatment with additional antibiotics for ongoing symptoms of cIAI; previously met criteria for failure; persisting/recurrent infection within abdomen; postsurgical wound infections included open wound with signs local infection i.e purulent exudates,erythema/warmth requires additional antibiotics &/or nonroutine wound care. Data of AUC(0-6)based on intensive sampling at Day4, is reported in this endpoint separately&only for those subjects who had clinical response of cure&failure at TOC visit. Here, 99999 signifies none of subjects had data. mMITTpopulation set used.‘n’ =subjects evaluable for this endpoint at specified categories.

End point type	Secondary

End point timeframe:

Plasma samples collection for AUC0-6 at: predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4 assessed for subjects with cure and failure at Test of Cure Visit (up to a maximum of 28 days)

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: hr*mcg/mL				
geometric mean (geometric coefficient of variation)				

Clinical Cure (n = 8, 1)	245.3 (± 41.4)	292.7 (± 99999)		
Clinical Failure (n = 2, 0)	378.0 (± 77.0)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) of Avibactam (AVI) for Subjects With Clinical Cure and Failure at TOC Visit: Intensive Sampling at Day 4 (mMITT Population)

End point title	Area Under the Plasma Concentration Time Curve From Time Zero up to 6 Hours (AUC[0-6]) of Avibactam (AVI) for Subjects With Clinical Cure and Failure at TOC Visit: Intensive Sampling at Day 4 (mMITT Population)

End point description:

AUC(0-6):area under plasma concentration-time curve from time 0upto 6hrs. Clinical cure:complete resolution/significant improvement signs&symptoms of index infection(cIAI) i.e no antimicrobial therapy,drainage/surgical intervention necessary&doesn't meet failure criteria. Failure:death related to intraabdominal infection; received treatment with additional antibiotics for ongoing symptoms of cIAI; previously met criteria for failure; persisting/recurrent infection within abdomen; postsurgical wound infections included open wound with signs local infection i.e purulent exudates,erythema/warmth requires additional antibiotics &/or nonroutine wound care. Data of AUC(0-6)based on intensive sampling at Day4, is reported in this endpoint separately&only for those subjects who had clinical response of cure&failure at TOC visit. Here, 99999 signifies none of subjects had data. mMITTpopulation set used.'n' =subjects evaluable for this endpoint at specified categories.

End point type	Secondary

End point timeframe:

Plasma samples collection for AUC0-6 at: predose, 0.5 1, 2, 3, 3.25, 3.5, 3.75, 4, 5 and 6 hour postdose on Day 4 assessed for subjects with cure and failure at Test of Cure Visit (up to a maximum of 28 days)

End point values	Aztreonam-Avibactam(ATM-AVI)+Metronidazole:Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
Clinical Cure (n = 8, 1)	42401.9 (± 41.9)	60302.1 (± 99999)		
Clinical Failure (n = 2, 0)	75509.9 (± 84.3)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to the LFU visit (up to maximum of 38 days)

Adverse event reporting additional description:

Same event may appear as AE and SAE, what is presented are distinct events. Event may be categorized as serious in 1 subject and as non-serious in another subject or 1 subject may have experienced both serious and non-serious event during study. Analysis was performed on safety population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	ATM-AVI+ Metronidazole: Low AVI Dose Cohort

Reporting group description:

Subjects with normal renal function or mild renal impairment (CrCl > 50 mL/min), received IV infusion of 500 mg ATM plus 137 mg AVI over 30 minutes as loading dose, followed by maintenance infusions of 1500 mg ATM plus 410 mg AVI, over a 3 hour period every 6 hours, for a minimum of 5 days and up to maximum of 14 days. Subjects also received 1 hour IV infusion of 500 mg metronidazole, every 8 hrs after first ATM-AVI maintenance infusion for a minimum of 5 days and up to maximum of 14 days. All study therapies could be discontinued (after at least 5 full days of IV therapy) at the discretion of the investigator.

Reporting group title	ATM-AVI + Metronidazole: High AVI Dose Cohort

Reporting group description:

Subjects received ATM-AVI IV infusion in following manner (1. normal renal function or mild renal impairment [CrCl >50mL/min] : 500 mg ATM plus 167 mg AVI over 30 minutes as loading dose, followed by maintenance infusions of 1500 mg ATM plus 500 mg AVI, over a 3 hour period every 6 hours; 2. moderate renal impairment [CrCl 31-50 ml/min]: 500 mg ATM plus 167 mg AVI over 30 minutes as loading dose, followed by IV extended loading infusion of 1500 mg ATM plus 500 mg AVI over 3 hour, followed by maintenance infusions of 750 mg ATM plus 250 mg AVI, over 3 hour period every 6 hours) along with 1 hour IV infusion of 500 mg metronidazole, every 8 hrs after first ATM-AVI maintenance infusion. All treatments were administered for minimum 5 days and up to maximum of 14 days. All study therapies could be discontinued (after at least 5 full days of IV therapy) at the discretion of the investigator.

Serious adverse events	ATM-AVI+ Metronidazole: Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 16 (25.00%)	5 / 18 (27.78%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intra-abdominal haematoma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Haemorrhage subcutaneous			

subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	ATM-AVI+ Metronidazole: Low AVI Dose Cohort	ATM-AVI + Metronidazole: High AVI Dose Cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 16 (62.50%)	10 / 18 (55.56%)	
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	0 / 16 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Testicular swelling			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	

Psychiatric disorders Confusional state subjects affected / exposed occurrences (all) Hallucination, visual subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1	 0 / 18 (0.00%) 0 0 / 18 (0.00%) 0	
Investigations Hepatic enzyme increased subjects affected / exposed occurrences (all)	 7 / 16 (43.75%) 7	 2 / 18 (11.11%) 2	
Injury, poisoning and procedural complications Limb injury subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0	 1 / 18 (5.56%) 1	
Cardiac disorders Cardiac failure congestive subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1	 0 / 18 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0	 1 / 18 (5.56%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytosis subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1	 2 / 18 (11.11%) 2 0 / 18 (0.00%) 0	
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0	 1 / 18 (5.56%) 1	
Gastrointestinal disorders Abdominal pain lower subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0	 2 / 18 (11.11%) 2	

Diarrhoea			
subjects affected / exposed	2 / 16 (12.50%)	3 / 18 (16.67%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Paraesthesia oral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Skin exfoliation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Chronic hepatitis C			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pneumonia			

subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2016	Addition of new sponsor study code. Describe the ATM-AVI dosing regimen for subjects with moderate renal impairment more in detail, especially with regard to the total daily doses. Updation of information on the expected end date of the study period. Clarification of pregnancy report time frame and process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported