# Clinical trial results:
# A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Efficacy and Safety of Intravenous CXA-201 with that of Meropenem in Complicated Intraabdominal Infections

## Summary

| | |
|---|---|
| EudraCT number | 2011-002120-41 |
| Trial protocol | HU DE PL BG LT EE LV |
| Global end of trial date | 15 October 2013 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 13 April 2016 |
| First version publication date | 05 August 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CXA-cIAI-10-08 and CXA-cIAI-10-09 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01445678 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Cubist Pharmaceuticals, Inc. |
| Sponsor organisation address | 65 Hayden Drive, Lexington, MA, United States, |
| Public contact | Medical Director, Cubist Pharmaceuticals, Inc., 001 781-860-8660, |
| Scientific contact | Medical Director, Cubist Pharmaceuticals, Inc., 001 781-860-8660, |

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 | 18 March 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 October 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This is a Phase 3, multicenter, prospective, randomized, double-blind, double dummy study of CXA-201 intravenous (IV) infusions to demonstrate the noninferiority of ceftolozane/tazobactam (CXA-201) plus metronidazole versus meropenem in adult subjects with complicated intraabdominal infections (cIAI).

Two identical Phase 3 protocol were initiated: CXA-cIAI-10-09 (2011-002120-41) and CXA-cIAI-10-08 (2011-002119-27). Based on this guidance and following scientific advice from the CHMP (Procedure No.: EMEA/H/SA/2181/2/2012/II; taking into account existing CHMP guidance) and agreement from the US FDA, Cubist revised its clinical development program for ceftolozane/tazobactam (CXA-201) leading to a single-study approval pathway for each indication.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonisation (ICH) Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 December 2011 |
| 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 | United States: 55 |
| Country: Number of subjects enrolled | Argentina: 75 |
| Country: Number of subjects enrolled | Australia: 3 |
| Country: Number of subjects enrolled | Belgium: 7 |
| Country: Number of subjects enrolled | Brazil: 4 |
| Country: Number of subjects enrolled | Bulgaria: 24 |
| Country: Number of subjects enrolled | Chile: 2 |
| Country: Number of subjects enrolled | Colombia: 10 |
| Country: Number of subjects enrolled | Croatia: 13 |
| Country: Number of subjects enrolled | Estonia: 75 |
| Country: Number of subjects enrolled | Georgia: 31 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Hungary: 65 |
| Country: Number of subjects enrolled | Israel: 11 |
| Country: Number of subjects enrolled | Latvia: 74 |
| Country: Number of subjects enrolled | Lithuania: 70 |

| | |
|---|---|
| Country: Number of subjects enrolled | Mexico: 20 |
| Country: Number of subjects enrolled | Moldova, Republic of: 31 |
| Country: Number of subjects enrolled | Peru: 13 |
| Country: Number of subjects enrolled | Poland: 39 |
| Country: Number of subjects enrolled | Romania: 109 |
| Country: Number of subjects enrolled | Russian Federation: 51 |
| Country: Number of subjects enrolled | Serbia: 29 |
| Country: Number of subjects enrolled | Slovakia: 47 |
| Country: Number of subjects enrolled | South Africa: 4 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 32 |
| Country: Number of subjects enrolled | Spain: 23 |
| Country: Number of subjects enrolled | Ukraine: 73 |
| Worldwide total number of subjects | 994 |
| EEA total number of subjects | 550 |

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) | 770 |
| From 65 to 84 years | 215 |
| 85 years and over | 9 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subjects enrolled in this study were at least 18 years of age with a complicated intra-abdominal infection. Subjects were eligible to participate in the study if they met all of the inclusion criteria and none of the exclusion criteria at the Screening visit.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | CXA-201 and Metronidazole as treatment for cIAI |

Arm description:

CXA-201 and metronidazole: CXA-201 IV infusion (ceftolozane 1000 milligrams [mg] + tazobactam 500 mg q8h) and metronidazole IV infusion (500 mg q8h) for 4 to 14 days.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ceftolozane/ Tazobactam |
| Investigational medicinal product code | |
| Other name | CXA-201 |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

CXA-201 intravenous (IV) infusion (ceftolozane 1000 milligrams [mg] and tazobactam 500 mg q8h) for 4 to 14 days

| | |
|---|---|
| Investigational medicinal product name | Metronidazole |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Metronidazole IV infusion (500 mg q 8h) for 4 to 14 days

| | |
|---|---|
| **Arm title** | Meropenem as treatment for cIAI |

Arm description:

Meropenem: Meropenem IV infusion (1000 mg q8h) for 4-14 days

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Meropenem |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Meropenem: Meropenem IV infusion (1000mg q8h) for 4-14 days Of the 979 treated subjects in the integrated analysis set, 497 received meropenem.

| **Number of subjects in period 1** | CXA-201 and Metronidazole as treatment for cIAI | Meropenem as treatment for cIAI |
|---|---|---|
| Started | 488 | 506 |
| Received at least 1 dose of study drug | 482 | 497 |
| Completed | 452 | 476 |
| Not completed | 36 | 30 |
| Physician decision | 1 | - |
| Consent withdrawn by subject | 11 | 7 |
| Adverse event, non-fatal | 12 | 8 |
| Lost to follow-up | 8 | 5 |
| Reason not specified | 2 | 2 |
| Lack of informed consent | - | 2 |
| Protocol deviation | 2 | 4 |
| Lack of efficacy | - | 2 |

## Baseline characteristics

### Reporting groups

| Reporting group title | CXA-201 and Metronidazole as treatment for cIAI |
|---|---|

Reporting group description:

CXA-201 and metronidazole: CXA-201 IV infusion (ceftolozane 1000 milligrams [mg] + tazobactam 500 mg q8h) and metronidazole IV infusion (500 mg q8h) for 4 to 14 days.

| Reporting group title | Meropenem as treatment for cIAI |
|---|---|

Reporting group description:

Meropenem: Meropenem IV infusion (1000 mg q8h) for 4-14 days

| Reporting group values | CXA-201 and Metronidazole as treatment for cIAI | Meropenem as treatment for cIAI | Total |
|---|---|---|---|
| Number of subjects | 488 | 506 | |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br>50.6<br>± 17.94 | <br><br>50.5<br>± 16.85 | <br><br><br>- |
| Gender, Male/Female<br>Units: participants | | | |
| Male<br>Female | | | 0<br>0 |

### Subject analysis sets

| Subject analysis set title | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--MITT population |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Microbiological intention-to-treat (MITT): all randomised subjects, regardless of whether or not the subjects went on to receive study drug, who had intra-abdominal infection (IAI) as evidenced by identification of at least 1 baseline intra-abdominal pathogen, regardless of susceptibility to study drug.

| Subject analysis set title | Meropenem--MITT population |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Microbiological intention-to-treat (MITT): all randomised subjects, regardless of whether or not the subjects went on to receive study drug, who had intra-abdominal infection (IAI) as evidenced by identification of at least 1 baseline intra-abdominal pathogen, regardless of susceptibility to study drug.

| Subject analysis set title | Ceftolozane/Tazobactam (CXA-201) +Metronidazole--CE population |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The clinically evaluable (CE) population was a subset of the intention-to-treat (ITT) population of subjects who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a test-of-cure (TOC) visit within the specified visit window. Subjects in this population had no confounding factors that interfered with the assessment of outcome and met the key inclusion/exclusion criteria and additional protocol-defined criteria.

| | |
|---|---|
| Subject analysis set title | Meropenem--CE population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The CE population was a subset of the intention-to-treat (ITT) population of subjects who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a test-of-cure (TOC) visit within the specified visit window. Subjects in this population had no confounding factors that interfered with the assessment of outcome and met the key inclusion/exclusion criteria and additional protocol-defined criteria.

| | |
|---|---|
| Subject analysis set title | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--ITT population |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT population consisted of all randomised subjects regardless of whether or not the subjects went on to receive study drug. Subjects in the ITT population were categorised based on the treatment that the subjects were randomised to, irrespective of what they actually received.

| | |
|---|---|
| Subject analysis set title | Meropenem--ITT population |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT population consisted of all randomised subjects regardless of whether or not the subjects went on to receive study drug. Subjects in the ITT population were categorised based on the treatment that the subjects were randomised to, irrespective of what they actually received.

| | |
|---|---|
| Subject analysis set title | Ceftolozane/ Tazobactam(CA-201)+Met-expanded ME population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The expanded microbiologically evaluable (ME) population consisted of all subjects in the MITT population who met all CE population criteria.

| | |
|---|---|
| Subject analysis set title | Meropenem--expanded ME population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The expanded ME population consisted of all subjects in the MITT population who met all CE population criteria.

| | |
|---|---|
| Subject analysis set title | Ceftolozane/ Tazobactam(CXA-201)+ Metronidazole--ME population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The ME population was the subset of CE subjects who had at least 1 baseline infecting pathogen identified that was susceptible to study drug. For subjects receiving nonstudy antibiotics with only Gram-positive activity, the per-pathogen outcome for Gram-positive organisms was indeterminate.

| | |
|---|---|
| Subject analysis set title | Meropenem--ME population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The ME population was the subset of CE subjects who had at least 1 baseline infecting pathogen identified that was susceptible to study drug. For subjects receiving nonstudy antibiotics with only Gram-positive activity, the per-pathogen outcome for Gram-positive organisms was indeterminate.

| **Reporting group values** | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--MITT population | Meropenem--MITT population | Ceftolozane/Tazobactam (CXA-201) +Metronidazole--CE population |
|---|---|---|---|
| Number of subjects | 389 | 417 | 375 |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 50.8 | 50.4 | |
| standard deviation | ± 18.25 | ± 16.87 | ± |

| | | | |
|---|---|---|---|
| Gender, Male/Female<br>Units: participants | | | |
| Male | 218 | 248 | |
| Female | 171 | 169 | |

| **Reporting group values** | Meropenem--CE population | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--ITT population | Meropenem--ITT population |
|---|---|---|---|
| Number of subjects | 399 | 476 | 494 |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | ± | ± | ± |
| Gender, Male/Female<br>Units: participants | | | |
| Male | | | |
| Female | | | |

| **Reporting group values** | Ceftolozane/Tazobactam(CA-201)+Met-expanded ME population | Meropenem--expanded ME population | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--ME population |
|---|---|---|---|
| Number of subjects | 307 | 345 | 275 |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | ± | ± | ± |
| Gender, Male/Female<br>Units: participants | | | |
| Male | | | |
| Female | | | |

| **Reporting group values** | Meropenem--ME population | | |
|---|---|---|---|
| Number of subjects | 321 | | |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | ± | | |
| Gender, Male/Female<br>Units: participants | | | |
| Male | | | |
| Female | | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | CXA-201 and Metronidazole as treatment for cIAI |

Reporting group description:

CXA-201 and metronidazole: CXA-201 IV infusion (ceftolozane 1000 milligrams [mg] + tazobactam 500 mg q8h) and metronidazole IV infusion (500 mg q8h) for 4 to 14 days.

| | |
|---|---|
| Reporting group title | Meropenem as treatment for cIAI |

Reporting group description:

Meropenem: Meropenem IV infusion (1000 mg q8h) for 4-14 days

| | |
|---|---|
| Subject analysis set title | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--MITT population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Microbiological intention-to-treat (MITT): all randomised subjects, regardless of whether or not the subjects went on to receive study drug, who had intra-abdominal infection (IAI) as evidenced by identification of at least 1 baseline intra-abdominal pathogen, regardless of susceptibility to study drug.

| | |
|---|---|
| Subject analysis set title | Meropenem--MITT population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Microbiological intention-to-treat (MITT): all randomised subjects, regardless of whether or not the subjects went on to receive study drug, who had intra-abdominal infection (IAI) as evidenced by identification of at least 1 baseline intra-abdominal pathogen, regardless of susceptibility to study drug.

| | |
|---|---|
| Subject analysis set title | Ceftolozane/Tazobactam (CXA-201) +Metronidazole--CE population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The clinically evaluable (CE) population was a subset of the intention-to-treat (ITT) population of subjects who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a test-of-cure (TOC) visit within the specified visit window. Subjects in this population had no confounding factors that interfered with the assessment of outcome and met the key inclusion/exclusion criteria and additional protocol-defined criteria.

| | |
|---|---|
| Subject analysis set title | Meropenem--CE population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The CE population was a subset of the intention-to-treat (ITT) population of subjects who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a test-of-cure (TOC) visit within the specified visit window. Subjects in this population had no confounding factors that interfered with the assessment of outcome and met the key inclusion/exclusion criteria and additional protocol-defined criteria.

| | |
|---|---|
| Subject analysis set title | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--ITT population |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT population consisted of all randomised subjects regardless of whether or not the subjects went on to receive study drug. Subjects in the ITT population were categorised based on the treatment that the subjects were randomised to, irrespective of what they actually received.

| | |
|---|---|
| Subject analysis set title | Meropenem--ITT population |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT population consisted of all randomised subjects regardless of whether or not the subjects went on to receive study drug. Subjects in the ITT population were categorised based on the treatment that the subjects were randomised to, irrespective of what they actually received.

| | |
|---|---|
| Subject analysis set title | Ceftolozane/ Tazobactam(CA-201)+Met-expanded ME population |

| | |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The expanded microbiologically evaluable (ME) population consisted of all subjects in the MITT population who met all CE population criteria.

| | |
|---|---|
| Subject analysis set title | Meropenem--expanded ME population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The expanded ME population consisted of all subjects in the MITT population who met all CE population criteria.

| | |
|---|---|
| Subject analysis set title | Ceftolozane/ Tazobactam(CXA-201)+ Metronidazole--ME population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The ME population was the subset of CE subjects who had at least 1 baseline infecting pathogen identified that was susceptible to study drug. For subjects receiving nonstudy antibiotics with only Gram-positive activity, the per-pathogen outcome for Gram-positive organisms was indeterminate.

| | |
|---|---|
| Subject analysis set title | Meropenem--ME population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The ME population was the subset of CE subjects who had at least 1 baseline infecting pathogen identified that was susceptible to study drug. For subjects receiving nonstudy antibiotics with only Gram-positive activity, the per-pathogen outcome for Gram-positive organisms was indeterminate.

## Primary: The percentage of subjects with clinical outcome of cure at the test of cure (TOC) visit in the clinically evaluable (CE) population

| | |
|---|---|
| End point title | The percentage of subjects with clinical outcome of cure at the test of cure (TOC) visit in the clinically evaluable (CE) population |

End point description:

Clinical cure is complete resolution or significant improvement in signs and symptoms of the index infection, such that no additional antibacterial therapy or surgical or drainage procedure was required for the index infection.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

TOC; 26-30 days after start of study drug administration

| End point values | Ceftolozane/Tazobactam (CXA-201) +Metronidazole --CE population | Meropenem--CE population | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 375[1] | 399[2] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Cure | 94.1 | 94 | | |
| Failure | 5.9 | 6 | | |

Notes:

[1] - CE population

[2] - CE population

## Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | Meropenem--CE population v Ceftolozane/Tazobactam (CXA-201) +Metronidazole--CE population |
| Number of subjects included in analysis | 774 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[3] |
| Parameter estimate | Percentage difference |
| Point estimate | 0 |
| Confidence interval | |
| level | Other: 99 % |
| sides | 2-sided |
| lower limit | -4.16 |
| upper limit | 4.3 |

Notes:

[3] - The hypotheses were tested at the 1-sided 0.005 significance level, through a 2-sided 99% confidence interval (CI) approach. The 2-sided 99% CI on the difference of proportions for ceftolozane/tazobactam plus metronidazole minus comparator (meropenem) was constructed using stratified Newcombe CI with Minimum Risk weights. Noninferiority was concluded if the lower bound of the 2-sided 99% CI was greater than minus 12.5%, in the CE population.

## Secondary: The percentage of subjects with clinical outcome of cure at the TOC visit in the intention-to-treat (ITT) Population

| End point title | The percentage of subjects with clinical outcome of cure at the TOC visit in the intention-to-treat (ITT) Population |
|---|---|

End point description:

Clinical cure is complete resolution or significant improvement in signs and symptoms of the index infection, such that no additional antibacterial therapy or surgical or drainage procedure was required for the index infection.

| End point type | Secondary |
|---|---|

End point timeframe:

TOC; 26-30 days after start of study drug administration

| End point values | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--ITT population | Meropenem--ITT population | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 476[4] | 494[5] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Cure | 83.8 | 85.8 | | |
| Failure | 16.2 | 14.2 | | |

Notes:

[4] - ITT population

[5] - ITT population

## Statistical analyses

| Statistical analysis title | Statistial Analysis |
|---|---|

Statistical analysis description:

The hypotheses were tested at the 1-sided 0.005 significance level, through a 2-sided 99% confidence

interval (CI) approach. The 2-sided 99% CI on the difference of proportions for ceftolozane/tazobactam plus metronidazole minus comparator (meropenem) was constructed using stratified Newcombe CI with Minimum Risk weights as described. Noninferiority was concluded if the lower bound of the 2-sided 99% CI was greater than minus 12.5%, in the the ITT population

| | |
|---|---|
| Comparison groups | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--ITT population v Meropenem--ITT population |
| Number of subjects included in analysis | 970 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Percentage difference |
| Point estimate | -2.2 |
| Confidence interval | |
| level | Other: 99 % |
| sides | 2-sided |
| lower limit | -7.95 |
| upper limit | 3.44 |

## Secondary: The percentage of subjects with clinical outcome of cure at the test of cure (TOC) visit in the microbiologically evaluable (ME), MITT, and expanded ME population

| | |
|---|---|
| End point title | The percentage of subjects with clinical outcome of cure at the test of cure (TOC) visit in the microbiologically evaluable (ME), MITT, and expanded ME population |

End point description:

Clinical cure is complete resolution or significant improvement in signs and symptoms of the index infection, such that no additional antibacterial therapy or surgical or drainage procedure was required for the index infection.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

TOC; 26-30 days after start of study drug administration

| End point values | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--MITT population | Meropenem--MITT population | Ceftolozane/Tazobactam(CA-201)+Met-expanded ME population | Meropenem--expanded ME population |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 389[6] | 417[7] | 307[8] | 345[9] |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Cure | 83 | 87.3 | 93.8 | 93.6 |
| Failure | 17 | 12.7 | 6.2 | 6.4 |

Notes:

[6] - MITT

[7] - MITT

[8] - Expanded ME

[9] - Expanded ME

| End point values | Ceftolozane/Tazobactam | Meropenem--ME population | | |
|---|---|---|---|---|

| | (CXA-201)+ Metronidazole--ME population | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 275[10] | 321[11] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Cure | 94.2 | 94.7 | | |
| Failure | 5.8 | 5.3 | | |

Notes:

[10] - ME population

[11] - ME population

### Statistical analyses

No statistical analyses for this end point

## Secondary: The percentage of subjects with microbiological success at the TOC visit in the MITT, ME, and expanded ME populations

| End point title | The percentage of subjects with microbiological success at the TOC visit in the MITT, ME, and expanded ME populations |
|---|---|

End point description:

An overall microbiological response was determined for each subject based on individual microbiological responses for each baseline pathogen at the TOC visit. In order for the subject to have a favourable overall microbiological response (ie, success), each baseline pathogen must have had a favourable microbiological outcome. If the outcome for any pathogen was unfavourable, the subject was considered an overall microbiological failure.

| End point type | Secondary |
|---|---|

End point timeframe:

TOC visit; 26-30 days after start of study drug administration

| End point values | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--MITT population | Meropenem--MITT population | Ceftolozane/Tazobactam(CA-201)+Met-expanded ME population | Meropenem--expanded ME population |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 389[12] | 417[13] | 307[14] | 345[15] |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Microbiological success | 85.3 | 88.7 | 95.4 | 94.5 |
| Microbiological failure | 6.4 | 6.7 | 4.6 | 5.5 |

Notes:

[12] - MITT population

[13] - MITT population

[14] - Expanded ME population

[15] - Expanded ME population

| End point values | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--ME population | Meropenem--ME population | | |
|---|---|---|---|---|

| Subject group type | Subject analysis set | Subject analysis set | | |
|---|---|---|---|---|
| Number of subjects analysed | 275[16] | 321[17] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Microbiological success | 96 | 95.6 | | |
| Microbiological failure | 4 | 4.4 | | |

Notes:

[16] - ME population

[17] - ME population

### Statistical analyses

No statistical analyses for this end point

## Secondary: The percentage of subjects with a gram-negative aerobes microbiological response at the TOC visit in the ME population

| End point title | The percentage of subjects with a gram-negative aerobes microbiological response at the TOC visit in the ME population |
|---|---|

End point description:

A microbiological response for gram-negative aerobes isolated at baseline at both the EOT and TOC visits. Microbiological response categories were eradication, presumed eradication, persistence, persistence acquiring resistance, presumed persistence, and indeterminate. Favourable microbiological responses included "eradication" or "presumed eradication." Unfavourable responses were considered "persistence," "persistence acquiring resistance," and "presumed persistence."

| End point type | Secondary |
|---|---|

End point timeframe:

End of treatment (EOT) through TOC; 26-30 days after start of study drug administration

| **End point values** | Ceftolozane/ Tazobactam(CXA-201)+ Metronidazole--ME population | Meropenem--ME population | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 243[18] | 282[19] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 96.3 | 95.4 | | |

Notes:

[18] - ME population

[19] - ME population

### Statistical analyses

No statistical analyses for this end point

## Secondary: The percentage of subjects with sustained clinical cure at LFU Visit in the CE, ITT, and ME populations

| End point title | The percentage of subjects with sustained clinical cure at LFU Visit in the CE, ITT, and ME populations |
|---|---|

End point description:

Sustained clinical cure at LFU is defined as no signs and symptoms recur or worsen since the TOC visit.

| End point type | Secondary |
|---|---|

End point timeframe:

Last follow up (LFU) visit; 38 to 45 days after first study drug administration

| **End point values** | Ceftolozane/Tazobactam (CXA-201) +Metronidazole --CE population | Meropenem--CE population | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--ITT population | Meropenem--ITT population |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 350[20] | 374[21] | 476[22] | 494[23] |
| Units: percentage of subjects | | | | |
| number (not applicable) | 100 | 99.5 | 83 | 85 |

Notes:

[20] - CE population with evaluable LFU data

[21] - CE population with evaluable LFU data

[22] - ITT population

[23] - ITT population

| **End point values** | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--ME population | Meropenem--ME population | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 258[24] | 304[25] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 100 | 99.3 | | |

Notes:

[24] - ME population with evaluable LFU data

[25] - ME population with evaluable LFU data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects with superinfections or new infections in the MITT population

| End point title | Percentage of subjects with superinfections or new infections in the MITT population |
|---|---|

End point description:

Superinfection outcome was defined as isolation of a pathogen, other than the original baseline pathogen(s), from an intra-abdominal specimen taken from a subject with signs or symptoms of infection while on study drug. A new infection was defined as isolation of a pathogen, other than the original baseline pathogen(s), from an intra-abdominal specimen in a subject with signs or symptoms of infection after treatment with study drug.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline through TOC visit

| End point values | Ceftolozane/Tazobactam(CXA-201)+Metronidazole--MITT population | Meropenem--MITT population | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 389[26] | 417[27] | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |
| Superinfection | 2.6 | 3.1 | | |
| New infection | 3.1 | 2.2 | | |

Notes:

[26] - MITT population

[27] - MITT population

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded for all subjects from the start of study drug administration through the last follow up visit, which occurred 38 to 45 days after the first dose of study drug.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Ceftolozane/Tazobactam + Metronidazole |
| Reporting group description: - | |
| Reporting group title | Meropenem |

Reporting group description: -

| Serious adverse events | Ceftolozane/Tazobactam + Metronidazole | Meropenem | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 39 / 482 (8.09%) | 36 / 497 (7.24%) | |
| number of deaths (all causes) | 11 | 8 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-abdominal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic venous thrombosis | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Sudden death | | | |
| subjects affected / exposed | 2 / 482 (0.41%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 3 / 482 (0.62%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Atrophic vulvovaginitis | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 2 / 497 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (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 | | | |

| | | | |
|---|---|---|---|
| Abdominal wound dehiscence | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia postoperative | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anastomotic leak | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumoconiosis | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Suture rupture | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound evisceration | | | |
| subjects affected / exposed | 2 / 482 (0.41%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |

| | | | |
|---|---|---|---|
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 2 / 482 (0.41%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Encephalopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Thrombocytosis | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocutaneous fistula | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal perforation | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 2 / 497 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal perforation | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 2 / 497 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal vein thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perforation bile duct | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary fistula | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 2 / 482 (0.41%) | 2 / 497 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendiceal abscess | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder abscess | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious peritonitis | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Graft infection | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 3 / 497 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lobar pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection pseudomonal | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pelvic abscess | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 2 / 497 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peridiverticular abscess | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 2 / 497 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 482 (0.62%) | 2 / 497 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Subdiaphragmatic abscess | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 2 / 497 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 482 (0.21%) | 0 / 497 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 482 (0.00%) | 1 / 497 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Ceftolozane/Tazobactam + Metronidazole | Meropenem | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 78 / 482 (16.18%) | 61 / 497 (12.27%) | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 25 / 482 (5.19%) | 20 / 497 (4.02%) | |
| occurrences (all) | 27 | 21 | |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 37 / 482 (7.68%) | 28 / 497 (5.63%) | |
| occurrences (all) | 40 | 31 | |
| Diarrhoea | | | |
| subjects affected / exposed | 30 / 482 (6.22%) | 25 / 497 (5.03%) | |
| occurrences (all) | 31 | 26 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

Cubist revised its clinical development program for ceftolozane/tazobactam leading to a single-study approval pathway for each indication, based guidance and following scientific advice from the CHMP and agreement from the US FDA.

Notes: