



Clinical trial results:

A Randomized, Active-Controlled Study to Evaluate the Efficacy and Safety of Intravenous Sulbactam-ETX2514 in the Treatment of Patients With Infections Caused by *Acinetobacter baumannii-calcoaceticus* Complex

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-002526-23 |
| Trial protocol | HU LT GR |
| Global end of trial date | 26 July 2021 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 12 October 2022 |
| First version publication date | 20 September 2022 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set This study was not prematurely ended and a full data set was introduced. |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | CS2514-2017-0004 |
|-----------------------|------------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Entasis Therapeutics |
| Sponsor organisation address | Gatehouse Park BioHub , 35 Gatehouse Drive , Waltham, United States, MA 02451 |
| Public contact | Chief Medical Officer, David Altarac, +1 781-810-0120, david.altarac@entasistx.com |
| Scientific contact | Chief Medical Officer, David Altarac, +1 781-810-0120, david.altarac@entasistx.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 | 18 March 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 July 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 July 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To compare the efficacy of ETX2514SUL plus imipenem/cilastatin to colistin plus imipenem/cilastatin in patients with carbapenem-resistant ABC (CRABC) infections in Part A;
- To compare the incidence of nephrotoxicity, as measured by the Risk-Injury-Failure-Loss-End stage renal disease (RIFLE) criteria, of ETX2514SUL to colistin in patients with ABC infections in Part A.

Protection of trial subjects:

All considerations regarding the protection of human subjects were carried out in accordance with the protocol, GCP, ICH Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements. The investigator (according to applicable regulatory requirements) or a person designated by the investigator and under the investigator's responsibility fully informed patients of all pertinent aspects of the clinical trial.

Background therapy: -

Evidence for comparator:

The combination regimen (colistin + imipenem / cilastatin) was considered acceptable as the comparator by the Committee for Medicinal Products for Human Use (CHMP) during the Scientific Advice held with Entasis Therapeutics in 2018.

Imipenem/cilastatin is a broad-spectrum beta-lactam antibiotic of the carbapenem class. Its bactericidal activity is against a broad spectrum of Gram-positive and Gram-negative bacteria, including anaerobic pathogens. The imipenem/cilastatin regimen (1g imipenem/1g cilastatin q6h infused over 60 mins) was considered acceptable by the CHMP as this is the maximum approved dose, making it appropriate for the patient population of the study. The dose adjustments by renal function are those in the EU imipenem SmPC.

Colistin by intravenous (IV) administration is indicated in adults and children including neonates for the treatment of serious infections due to selected aerobic Gram-negative pathogens in patients with limited treatment options. Colistin is administered according to the protocol at 5 mg/kg of colistin base activity (CBA) divided into 2 doses 12 hours apart. Doses are adjusted to ideal body weight in obese patients, and doses do not exceed 300 mg of CBA per day. A single loading dose of 5 mg/kg (total dose not exceeding 300 mg CBA) given IV over 30 to 60 minutes is administered on Day 1. Colistin infusions beyond the loading dose on Day 1 begins 12 hours after the initial loading dose and are infused over 30 minutes. This dose regime was also considered acceptable by the CHMP even if it might not result in all patients receiving a daily colistin dose that would be recommended in the EU SmPC.

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|---|-------------------|
| Actual start date of recruitment | 05 September 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Greece: 9 |
| Country: Number of subjects enrolled | Hungary: 17 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Lithuania: 5 |
| Country: Number of subjects enrolled | Belarus: 8 |
| Country: Number of subjects enrolled | Brazil: 3 |
| Country: Number of subjects enrolled | China: 47 |
| Country: Number of subjects enrolled | India: 4 |
| Country: Number of subjects enrolled | Israel: 16 |
| Country: Number of subjects enrolled | Mexico: 9 |
| Country: Number of subjects enrolled | Peru: 13 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Russian Federation: 36 |
| Country: Number of subjects enrolled | Thailand: 6 |
| Country: Number of subjects enrolled | Turkey: 9 |
| Country: Number of subjects enrolled | Taiwan: 22 |
| Country: Number of subjects enrolled | United States: 2 |
| Worldwide total number of subjects | 207 |
| EEA total number of subjects | 31 |

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) | 98 |
| From 65 to 84 years | 87 |
| 85 years and over | 22 |

Subject disposition

Recruitment

Recruitment details:

Eighty-five (85) clinical sites were activated, 71 clinical sites screened patients, and 59 clinical sites randomized/enrolled patients in Belarus, Brazil, China, Greece, Hungary, India, Israel, Lithuania, Mexico, Peru, Russia, South Korea, Taiwan, Thailand, Turkey, and the United States (US). From 05 September 2019 to 26 July 2021.

Pre-assignment

Screening details:

A known infection caused by ABC (bacteremia, HABP, VABP, VP, complicated urinary tract infection [cUTI] or acute pyelonephritis [AP], or surgical or post-traumatic wound infections).
A total of 531 patients were screened of which 324 (61%) were screen failures. The primary reason for screen failure was "Failure to meet inclusion/exclusion criteria

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

While study drugs were not masked due to logistical reasons, every attempt was made to maintain the blind for patients, all staff at the site, and the Sponsor or its designees, except for the treatment physician and other immediate healthcare providers.

Clinical outcome assessments were performed by a blinded assessor, in addition to the unblinded Investigator. Whenever possible, the same blinded assessor completed all clinical outcome assessments for a study patient.

Arms

| | |
|------------------------------|---------------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Part A - Group 1 - experimental group |

Arm description:

Part A was the pivotal, assessor-blind, randomized, comparative portion of the study in patients with documented ABC hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), ventilated pneumonia (VP), or bacteremia. While study drugs were not masked due to logistical reasons, every attempt was made to maintain the blind for patients, all staff at the site, and the Sponsor or its designees, except for the treatment physician and other immediate healthcare providers.

Group 1 (experimental): 1.0 g sulbactam/1.0 g durlobactam IV infused over 3 hours every 6 hours (q6h) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h;

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

Dosage and administration details:

1.0 g sulbactam IV infused over 3 hours every 6 hours (q6h).

Day 1 was defined as the first day of study drug administration. The subsequent study days were defined by the number of treatment days thereafter. Treatment days constituted 24 hours of treatment. For those patients with no dose adjustments, the duration of antibiotic treatment with study drug therapy was 28 doses of sulbactam-durlobactam plus 28 doses of imipenem/cilastatin (ie, treatment for 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated.

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

Dosage and administration details:

1.0 g durlobactam IV infused over 3 hours every 6 hours (q6h).

Day 1 was defined as the first day of study drug administration. The subsequent study days were defined by the number of treatment days thereafter. Treatment days constituted 24 hours of treatment. For those patients with no dose adjustments, the duration of antibiotic treatment with study drug therapy was 28 doses of sulbactam-durlobactam plus 28 doses of imipenem/cilastatin (ie, treatment for 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated.

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Imipenem/Cilastatin 500 mg/500 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

Day 1 was defined as the first day of study drug administration. The subsequent study days were defined by the number of treatment days thereafter. Treatment days constituted 24 hours of treatment. For those patients with no dose adjustments, the duration of antibiotic treatment with study drug therapy was 28 doses of sulbactam-durlobactam plus 28 doses of imipenem/cilastatin (ie, treatment for 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated.

| | |
|------------------|----------------------------------|
| Arm title | Part A - Group 2 - control group |
|------------------|----------------------------------|

Arm description:

Group 2 (control group): 2.5 mg/kg colistin IV infused over 30 minutes every 12 hours (after an initial loading dose of colistin 2.5 to 5 mg/kg) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | COLOMYCIN INJECTION 2 million IU/vial |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Colistin was administered at a daily dose of 5 mg/kg of CBA divided into 2 doses 12 hours apart. Doses were adjusted to ideal body weight in obese patients. Patients who weighed <60 kg with normal renal function received a flat dose of 300 mg CBA or 9 MIU/day. A single loading dose of 2.5 to 5 mg/kg (total dose not exceeding 300 mg CBA or 9 MIU and following local standard of care) given IV over 3 to 6 minutes (or according to standard of care) was administered on Day 1. Colistin infusions beyond the loading dose on Day 1 began 12 hours after the initial loading dose and were infused over 30 minutes.

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Imipenem/Cilastatin 500 mg/500 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

Day 1 was defined as the first day of study drug administration. The subsequent study days were defined by the number of treatment days thereafter. Treatment days constituted 24 hours of treatment.

For those patients with no dose adjustments, the duration of antibiotic treatment with study drug therapy was 28 doses of sulbactam-durlobactam plus 28 doses of imipenem/cilastatin (ie, treatment for 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated.

| | |
|------------------|------------------|
| Arm title | Part B - Group 3 |
|------------------|------------------|

Arm description:

Part B (Group 3) was the open-label, supportive portion of the study that included patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms resistant to colistin or polymyxin B, who failed a colistin or polymyxin B regimen prior to study entry or were on acute renal replacement therapy, and patients with infections due to colistin- or polymyxin B-resistant ABC with sources of infection other than HABP, VABP, VP, and/or bacteremia.

Group 3: 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

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

Dosage and administration details:

1.0 g sulbactam IV infused over 3 hours every 6 hours (q6h).

Day 1 was defined as the first day of study drug administration. The subsequent study days were defined by the number of treatment days thereafter. Treatment days constituted 24 hours of treatment. For those patients with no dose adjustments, the duration of antibiotic treatment with study drug therapy was 28 doses of sulbactam-durlobactam plus 28 doses of imipenem/cilastatin (ie, treatment for 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated.

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

Dosage and administration details:

1.0 g durlobactam IV infused over 3 hours every 6 hours (q6h).

Day 1 was defined as the first day of study drug administration. The subsequent study days were defined by the number of treatment days thereafter. Treatment days constituted 24 hours of treatment. For those patients with no dose adjustments, the duration of antibiotic treatment with study drug therapy was 28 doses of sulbactam-durlobactam plus 28 doses of imipenem/cilastatin (ie, treatment for 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated.

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Imipenem/Cilastatin 500 mg/500 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

Day 1 was defined as the first day of study drug administration. The subsequent study days were defined by the number of treatment days thereafter. Treatment days constituted 24 hours of treatment. For those patients with no dose adjustments, the duration of antibiotic treatment with study drug therapy was 28 doses of sulbactam-durlobactam plus 28 doses of imipenem/cilastatin (ie, treatment for 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated.

| Number of subjects in period 1^[1] | Part A - Group 1 - experimental group | Part A - Group 2 - control group | Part B - Group 3 |
|---|---------------------------------------|----------------------------------|------------------|
| Started | 92 | 89 | 28 |
| Completed | 69 | 61 | 22 |
| Not completed | 23 | 28 | 6 |
| Adverse event, serious fatal | 15 | 21 | 4 |
| Consent withdrawn by subject | 2 | 3 | 1 |
| No growth of ABC | 2 | 1 | - |
| Others | 1 | 1 | 1 |
| Adverse event, non-fatal | - | 1 | - |
| Transferred to other arm/group | 1 | 1 | - |
| Prohibited concomitant medication | 1 | - | - |
| Protocol deviation | 1 | - | - |

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.

Justification: Two (2) patients were transferred from Part A to part B. These patients were analyzed at each arm until/ from the time point of transfer. The number of patients who started in Part B (28) already includes the 2 patients transferred from Part A. the For this reason, the number of subjects transferring in and out of the arms in the period are not the same.

Baseline characteristics

Reporting groups

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|-----------------------|---------------------------------------|
| Reporting group title | Part A - Group 1 - experimental group |
|-----------------------|---------------------------------------|

Reporting group description:

Part A was the pivotal, assessor-blind, randomized, comparative portion of the study in patients with documented ABC hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), ventilated pneumonia (VP), or bacteremia. While study drugs were not masked due to logistical reasons, every attempt was made to maintain the blind for patients, all staff at the site, and the Sponsor or its designees, except for the treatment physician and other immediate healthcare providers.

Group 1 (experimental): 1.0 g sulbactam/1.0 g durlobactam IV infused over 3 hours every 6 hours (q6h) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h;

| | |
|-----------------------|----------------------------------|
| Reporting group title | Part A - Group 2 - control group |
|-----------------------|----------------------------------|

Reporting group description:

Group 2 (control group): 2.5 mg/kg colistin IV infused over 30 minutes every 12 hours (after an initial loading dose of colistin 2.5 to 5 mg/kg) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

| | |
|-----------------------|------------------|
| Reporting group title | Part B - Group 3 |
|-----------------------|------------------|

Reporting group description:

Part B (Group 3) was the open-label, supportive portion of the study that included patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms resistant to colistin or polymyxin B, who failed a colistin or polymyxin B regimen prior to study entry or were on acute renal replacement therapy, and patients with infections due to colistin- or polymyxin B-resistant ABC with sources of infection other than HABP, VABP, VP, and/or bacteremia.

Group 3: 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

| Reporting group values | Part A - Group 1 - experimental group | Part A - Group 2 - control group | Part B - Group 3 |
|---------------------------------------|---------------------------------------|----------------------------------|------------------|
| Number of subjects | 92 | 89 | 28 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 43 | 37 | 19 |
| From 65-84 years | 43 | 36 | 9 |
| 85 years and over | 6 | 16 | 0 |
| Gender categorical Units: Subjects | | | |
| Female | 24 | 23 | 7 |
| Male | 68 | 66 | 21 |

| Reporting group values | Total | | |
|---------------------------------------|-------|--|--|
| Number of subjects | 207 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 98 | | |
| From 65-84 years | 87 | | |
| 85 years and over | 22 | | |
| Gender categorical Units: Subjects | | | |
| Female | 52 | | |
| Male | 155 | | |

End points

End points reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Part A - Group 1 - experimental group |
|-----------------------|---------------------------------------|

Reporting group description:

Part A was the pivotal, assessor-blind, randomized, comparative portion of the study in patients with documented ABC hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), ventilated pneumonia (VP), or bacteremia. While study drugs were not masked due to logistical reasons, every attempt was made to maintain the blind for patients, all staff at the site, and the Sponsor or its designees, except for the treatment physician and other immediate healthcare providers.

Group 1 (experimental): 1.0 g sulbactam/1.0 g durlobactam IV infused over 3 hours every 6 hours (q6h) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h;

| | |
|-----------------------|----------------------------------|
| Reporting group title | Part A - Group 2 - control group |
|-----------------------|----------------------------------|

Reporting group description:

Group 2 (control group): 2.5 mg/kg colistin IV infused over 30 minutes every 12 hours (after an initial loading dose of colistin 2.5 to 5 mg/kg) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

| | |
|-----------------------|------------------|
| Reporting group title | Part B - Group 3 |
|-----------------------|------------------|

Reporting group description:

Part B (Group 3) was the open-label, supportive portion of the study that included patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms resistant to colistin or polymyxin B, who failed a colistin or polymyxin B regimen prior to study entry or were on acute renal replacement therapy, and patients with infections due to colistin- or polymyxin B-resistant ABC with sources of infection other than HABP, VABP, VP, and/or bacteremia.

Group 3: 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

| | |
|----------------------------|---|
| Subject analysis set title | CRABC m-MITT Population in Part A-Group 1 |
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|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

For Part A, the CRABC m-MITT Population included patients who met m-MITT criteria and had a baseline ABC organism that was confirmed to be carbapenem-resistant (MIC of imipenem/meropenem ≥ 8 ug/mL) by the central laboratory or by the local laboratory if the central laboratory was not able to characterize the isolate for any reason. Patients were excluded from the CRABC m-MITT Population if they had isolates that were deemed by the central laboratory to be resistant to sulbactam-durlobactam (MIC >4 ug/mL) or colistin (MIC ≥ 4 ug/mL), if their blood culture or respiratory samples were collected more than 72 hours prior to randomization, if they were transferred from Part A to Part B, or if they were enrolled with infections other than ABC pneumonia or bloodstream infection (ie, ABC infections other than HABP, VABP, VP, and bacteremia). Patients were enrolled until there were at least 120 patients in the CRABC Microbiologically Modified Intent-to-Treat (MITT) (m-MITT) Population in Part A.

| | |
|----------------------------|---|
| Subject analysis set title | CRABC m-MITT Population in Part A-Group 2 |
|----------------------------|---|

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|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

For Part A, the CRABC m-MITT Population included patients who met m-MITT criteria and had a baseline ABC organism that was confirmed to be carbapenem-resistant (MIC of imipenem/meropenem ≥ 8 ug/mL) by the central laboratory or by the local laboratory if the central laboratory was not able to characterize the isolate for any reason. Patients were excluded from the CRABC m-MITT Population if they had isolates that were deemed by the central laboratory to be resistant to sulbactam-durlobactam (MIC >4 ug/mL) or colistin (MIC ≥ 4 ug/mL), if their blood culture or respiratory samples were collected more than 72 hours prior to randomization, if they were transferred from Part A to Part B, or if they were enrolled with infections other than ABC pneumonia or bloodstream infection (ie, ABC infections other than HABP, VABP, VP, and bacteremia). Patients were enrolled until there were at least 120 patients in the CRABC Microbiologically Modified Intent-to-Treat (MITT) (m-MITT) Population in Part A.

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | ITT Population - Part A - Group 1 |
|----------------------------|-----------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The ITT Population included all patients randomized to study drug treatment (sulbactam-durlobactam + imipenem/cilastatin or colistin + imipenem/cilastatin) in Part A or enrolled in Part B, regardless of whether the patient actually received study drug.

For Part A -Group 1, the total number of patients is 90 (excluding patients who withdrew consent).

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | ITT Population - Part A - Group 2 |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT Population included all patients randomized to study drug treatment (sulbactam-durlobactam + imipenem/cilastatin or colistin + imipenem/cilastatin) in Part A or enrolled in Part B, regardless of whether the patient actually received study drug.

For Part A -Group 2, the total number of patients is 85 (excluding patients who withdrew consent).

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | m-MITT - Part A - Group 1 |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

The Microbiologically Modified Intent-to-Treat (m-MITT) Population included patients who met MITT criteria and had an ABC organism isolated as the qualifying culture specimen, as confirmed by the central and/or local microbiology laboratory.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | m-MITT - Part A -Group 2 |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Microbiologically Modified Intent-to-Treat (m-MITT) Population included patients who met MITT criteria and had an ABC organism isolated as the qualifying culture specimen, as confirmed by the central and/or local microbiology laboratory.

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | CE Population - Part A - Group 1 |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

The Clinical Evaluable (CE) Population included patients who met m-MITT criteria and met evaluability criteria (met key inclusion criteria, did not meet key exclusion criteria, received at least 72 hours of study drug [ie, 12 doses of sulbactam-durlobactam plus 12 doses of imipenem/cilastatin or 6 doses of colistin plus 12 doses of imipenem/cilastatin in patients without dose adjustments] to be a clinical cure, received at least 48 hours of study drug [ie, 8 doses of sulbactam-durlobactam plus 8 doses of imipenem/cilastatin or 4 doses of colistin plus 8 doses of imipenem/cilastatin in patients without dose adjustments] to be a clinical failure, received $\geq 80\%$ of anticipated doses, and did not have a clinical response of indeterminate at the TOC Visit);

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | CE Population - Part A - Group 2 |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

The Clinical Evaluable (CE) Population included patients who met m-MITT criteria and met evaluability criteria (met key inclusion criteria, did not meet key exclusion criteria, received at least 72 hours of study drug [ie, 12 doses of sulbactam-durlobactam plus 12 doses of imipenem/cilastatin or 6 doses of colistin plus 12 doses of imipenem/cilastatin in patients without dose adjustments] to be a clinical cure, received at least 48 hours of study drug [ie, 8 doses of sulbactam-durlobactam plus 8 doses of imipenem/cilastatin or 4 doses of colistin plus 8 doses of imipenem/cilastatin in patients without dose adjustments] to be a clinical failure, received $\geq 80\%$ of anticipated doses, and did not have a clinical response of indeterminate at the TOC Visit);

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | ME Population - Part A -Group 1 |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Microbiologic Evaluable (ME) Population included patients who met m-MITT criteria and CE criteria and had an appropriately collected culture specimen and interpretable culture result when specimen collection was clinically indicated at the TOC Visit;

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | ME Population - Part A -Group 2 |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Microbiologic Evaluable (ME) Population included patients who met m-MITT criteria and CE criteria and had an appropriately collected culture specimen and interpretable culture result when specimen collection was clinically indicated at the TOC Visit;

| | |
|----------------------------|--|
| Subject analysis set title | CRABC ME Population - Part A - Group 1 |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The CRABC ME Population included patients who met ME criteria and who had a baseline ABC organism that was confirmed to be carbapenem-resistant (and susceptible to sulbactam-durlobactam for Parts A

and B and susceptible to colistin for Part A)

| | |
|----------------------------|--|
| Subject analysis set title | CRABC ME Population - Part A - Group 2 |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The CRABC ME Population included patients who met ME criteria and who had a baseline ABC organism that was confirmed to be carbapenem-resistant (and susceptible to sulbactam-durlobactam for Parts A and B and susceptible to colistin for Part A)

Primary: 28-day all-cause mortality in the CRABC m-MITT Population in Part A

| | |
|-----------------|---|
| End point title | 28-day all-cause mortality in the CRABC m-MITT Population in Part A |
|-----------------|---|

End point description:

The primary efficacy endpoint for the study was 28-day all-cause mortality in the CRABC m-MITT Population in Part A.

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

End point timeframe:

Day 28

| End point values | CRABC m-MITT Population in Part A-Group 1 | CRABC m-MITT Population in Part A-Group 2 | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 63 | 62 | | |
| Units: patients | 12 | 20 | | |

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | non-inferiority assessment |
|----------------------------|----------------------------|

Statistical analysis description:

The non-inferiority assessment was based on the 2-sided 95% CIs computed using a continuity-corrected Z-statistic for the difference ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]) in 28-day all-cause mortality rates between the treatment groups. Non-inferiority was concluded if the upper limit of the 2-sided 95% CI was less than +20%. Superiority was concluded if the upper limit of the 2-sided 95% CI was less than 0.

| | |
|---|---|
| Comparison groups | CRABC m-MITT Population in Part A-Group 2 v CRABC m-MITT Population in Part A-Group 1 |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Mean difference (net) |
| Point estimate | -13.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30 |
| upper limit | 3.5 |
| Variability estimate | Standard deviation |

Primary: Incidence of nephrotoxicity (RIFLE) - Part A

| | |
|-----------------|---|
| End point title | Incidence of nephrotoxicity (RIFLE) - Part A ^[1] |
|-----------------|---|

End point description:

Analysis of patients with nephrotoxicity as measured by RIFLE criteria at any post-baseline visit based on the Investigator's opinion for the Safety Population for Part A, excluding patients with chronic hemodialysis at baseline baseline.

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

End point timeframe:

At any post-baseline visit

Notes:

[1] - 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: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| End point values | Part A - Group 1 - experimental group | Part A - Group 2 - control group | | |
|-----------------------------|---------------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 85 | | |
| Units: patients | 12 | 32 | | |

Statistical analyses

| | |
|----------------------------|-------------------------------------|
| Statistical analysis title | Nephrotoxicity as Measured by RIFLE |
|----------------------------|-------------------------------------|

Statistical analysis description:

Percentage of patients

| | |
|---|--|
| Comparison groups | Part A - Group 1 - experimental group v Part A - Group 2 - control group |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.0002 ^[3] |
| Method | Chi-squared |

Notes:

[2] - p-value was obtained based on a Chi-Square test for treatment group differences

[3] - p-value was obtained based on a Chi-Square test for treatment group differences.

Secondary: 28-day all-cause mortality in the ITT Population PartA

| | |
|-----------------|--|
| End point title | 28-day all-cause mortality in the ITT Population PartA |
|-----------------|--|

End point description:

Sulbactam-durlobactam + imipenem/cilastatin met the secondary endpoint of 28-day all-cause mortality compared to colistin + imipenem/cilastatin in all other populations of Part A. The mortality rate in the sulbactam-durlobactam + imipenem/cilastatin group was 21.1% (19 of 90 patients) compared to 32.9% (28 of 85 patients) in the colistin + imipenem/cilastatin group (treatment difference of -11.8%; 95% CI: -26.0%, 2.4%) for the ITT Population (excluding patients who withdrew consent).

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 28 days | |

| End point values | ITT Population - Part A - Group 1 | ITT Population - Part A - Group 2 | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 90 | 85 | | |
| Units: patients | 19 | 28 | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|---|---|
| Comparison groups | ITT Population - Part A - Group 1 v ITT Population - Part A - Group 2 |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | -11.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26 |
| upper limit | 2.4 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at TOC in the CRABC m-MITT Population Part A

| | |
|--|--|
| End point title | Clinical cure at TOC in the CRABC m-MITT Population Part A |
| End point description: | A significant treatment difference of 21.6% (95% CI: 2.9%, 40.3%) in clinical cure at TOC was observed with 61.9% (39 of 63) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 40.3% (25 of 62) of patients in the colistin + imipenem/cilastatin group achieving clinical cure for the CRABC m-MITT Population, excluding patients who withdrew consent. |
| End point type | Secondary |
| End point timeframe: | |
| The Test of Cure (TOC) Visit was completed 7 days (± 2 days) after the end of treatment (EOT) Visit for all patients. | |

| End point values | CRABC m-MITT Population in Part A-Group 1 | CRABC m-MITT Population in Part A-Group 2 | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 63 | 62 | | |
| Units: patients | 39 | 25 | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|--|---|
| Statistical analysis description: | |
| Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | CRABC m-MITT Population in Part A-Group 1 v CRABC m-MITT Population in Part A-Group 2 |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 21.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.9 |
| upper limit | 40.3 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at TOC in the m-MITT Part A

| End point title | Clinical cure at TOC in the m-MITT Part A |
|--|---|
| End point description: | |
| A significant treatment difference of 25.2% (95% CI: 8.6, 41.7) in clinical cure at TOC was observed with 62.3% (48 of 77) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 37.2% (29 of 78) of patients in the colistin + imipenem/cilastatin group for the m-MITT Population | |
| End point type | Secondary |
| End point timeframe: | |
| The Test of Cure (TOC) Visit was completed 7 days (±2 days) after the EOT Visit for all patients. | |

| End point values | m-MITT - Part A - Group 1 | m-MITT - Part A -Group 2 | | |
|-----------------------------|------------------------------|-----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 | 78 | | |
| Units: patients | 48 | 29 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | m-MITT - Part A - Group 1 v m-MITT - Part A -Group 2 |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 25.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.6 |
| upper limit | 41.7 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at TOC in the CE population Part A

| | |
|--|--|
| End point title | Clinical cure at TOC in the CE population Part A |
| End point description: A significant treatment difference of 29.2% (95% CI: 10.8%, 47.6%) in clinical cure at TOC was observed with 67.2% (45 of 67) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 37.9% (22 of 58) of patients in the colistin + imipenem/cilastatin group for the CE Population. | |
| End point type | Secondary |
| End point timeframe: The Test of Cure (TOC) Visit was completed 7 days (±2 days) after the EOT Visit for all patients. | |

| End point values | CE Population - Part A - Group 1 | CE Population - Part A - Group 2 | | |
|-----------------------------|----------------------------------|----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 67 | 58 | | |
| Units: patients | 45 | 22 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | CE Population - Part A - Group 2 v CE Population - Part A - Group 1 |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 29.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.8 |
| upper limit | 47.6 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at TOC in the ME population Part A

| | |
|--|--|
| End point title | Clinical cure at TOC in the ME population Part A |
| End point description: A significant treatment difference of 31.7% (95% CI: 12.0%, 51.4%) in clinical cure at TOC was observed with 69.0% (40 of 58) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 37.3% (19 of 51) of patients in the colistin + imipenem/cilastatin group for the ME Population. | |
| End point type | Secondary |
| End point timeframe: The Test of Cure (TOC) Visit was completed 7 days (±2 days) after the EOT Visit for all patients | |

| End point values | ME Population - Part A -Group 1 | ME Population - Part A -Group 2 | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 58 | 51 | | |
| Units: patients | 40 | 19 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | ME Population - Part A -Group 1 v ME Population - Part A - Group 2 |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 31.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12 |
| upper limit | 51.4 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at TOC in the CRABC ME Population Part A

| | |
|--|--|
| End point title | Clinical cure at TOC in the CRABC ME Population Part A |
| End point description: A significant treatment difference of 31.0% (95% CI: 9.2%, 52.9%) in clinical cure at TOC was observed with 67.4% (31 of 46) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 36.4% (16 of 44) of patients in the colistin + imipenem/cilastatin group for the CRABC ME Population | |
| End point type | Secondary |
| End point timeframe: The Test of Cure (TOC) Visit was completed 7 days (± 2 days) after the EOT Visit for all patients. | |

| End point values | CRABC ME Population - Part A - Group 1 | CRABC ME Population - Part A - Group 2 | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 46 | 44 | | |
| Units: patients | 31 | 16 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | CRABC ME Population - Part A - Group 1 v CRABC ME Population - Part A - Group 2 |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.2 |
| upper limit | 52.9 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at EOT in the m-MITT population Part A

| | |
|---|--|
| End point title | Clinical cure at EOT in the m-MITT population Part A |
| End point description: | |
| A significant treatment difference of 29.2% (95% CI: 13.2%, 45.1%) in clinical cure at EOT was observed with 75.3% (58 of 77) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 46.2% (36 of 78) of patients in the colistin + imipenem/cilastatin group for the m-MITT Population in Part A | |
| End point type | Secondary |
| End point timeframe: | |
| At end of treatment (EOT) visit (\geq Day 7 \leq Day 14) | |

| End point values | m-MITT - Part A - Group 1 | m-MITT - Part A -Group 2 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 | 78 | | |
| Units: patients | 58 | 36 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Treatment Difference |
| Comparison groups | m-MITT - Part A -Group 2 v m-MITT - Part A - Group 1 |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| Parameter estimate | Mean difference (net) |
| Point estimate | 29.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.2 |
| upper limit | 45.1 |
| Variability estimate | Standard deviation |

Notes:

[4] - Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic.

Secondary: Clinical cure at EOT in the CRABC m-MITT population Part A

| | |
|--|--|
| End point title | Clinical cure at EOT in the CRABC m-MITT population Part A |
| End point description: A significant treatment difference of 29.4% (95% CI: 11.4%, 47.4%) in clinical cure at EOT was observed with 74.6% (47 of 63) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 45.2% (28 of 62) of patients in the colistin + imipenem/cilastatin group for the CRABC m-MITT Population excluding patients who withdrew consent. | |
| End point type | Secondary |
| End point timeframe: At end of treatment (EOT) visit (\geq Day 7 \leq Day 14) | |

| End point values | CRABC m-MITT Population in Part A-Group 1 | CRABC m-MITT Population in Part A-Group 2 | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 63 | 62 | | |
| Units: patients | 47 | 28 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | CRABC m-MITT Population in Part A-Group 1 v CRABC m-MITT Population in Part A-Group 2 |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 29.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.4 |
| upper limit | 47.4 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at EOT in the CE population Part A

| | |
|-----------------|--|
| End point title | Clinical cure at EOT in the CE population Part A |
|-----------------|--|

End point description:

A significant treatment difference of 29.6% (95% CI: 11.6%, 47.6%) in clinical cure at EOT was observed with 76.1% (51 of 67) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 46.6% (27 of 58) of patients in the colistin + imipenem/cilastatin group for the CE Population in Part A

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

End point timeframe:

At end of treatment (EOT) visit (\geq Day 7 \leq Day 14)

| End point values | CE Population - Part A - Group 1 | CE Population - Part A - Group 2 | | |
|-----------------------------|----------------------------------|----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 67 | 58 | | |
| Units: patients | 51 | 27 | | |

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Treatment Difference |
|----------------------------|----------------------|

Statistical analysis description:

Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic.

| | |
|---|---|
| Comparison groups | CE Population - Part A - Group 1 v CE Population - Part A - Group 2 |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 29.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.6 |
| upper limit | 47.6 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at EOT in the ME population Part A

| | |
|-----------------|--|
| End point title | Clinical cure at EOT in the ME population Part A |
|-----------------|--|

End point description:

A significant treatment difference of 30.5% (95% CI: 11.3%, 49.8%) in clinical cure at EOT was observed with 77.6% (45 of 58) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 47.1% (24 of 51) of patients in the colistin + imipenem/cilastatin group for the ME Population in Part A.

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

End point timeframe:

At end of treatment (EOT) visit (\geq Day 7 \leq Day 14)

| End point values | ME Population - Part A -Group 1 | ME Population - Part A -Group 2 | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 58 | 51 | | |
| Units: patients | 45 | 24 | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|--|--|
| Statistical analysis description: | |
| Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | ME Population - Part A -Group 2 v ME Population - Part A - Group 1 |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 30.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.3 |
| upper limit | 49.8 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at EOT in the CRABC ME population Part A

| | |
|---|--|
| End point title | Clinical cure at EOT in the CRABC ME population Part A |
| End point description: | |
| A significant treatment difference of 30.7% (95% CI: 9.1%, 52.3%) in clinical cure at EOT was observed with 73.9% (34 of 46) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 43.2% (19 of 44) of patients in the colistin + imipenem/cilastatin group for the CRABC ME Population in Part A. | |
| End point type | Secondary |
| End point timeframe: | |
| At end of treatment (EOT) visit (\geq Day 7 \leq Day 14) | |

| End point values | CRABC ME Population - Part A - Group 1 | CRABC ME Population - Part A - Group 2 | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 46 | 44 | | |
| Units: patients | 34 | 19 | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|--|---|
| Statistical analysis description: | |
| Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | CRABC ME Population - Part A - Group 1 v CRABC ME Population - Part A - Group 2 |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 30.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.1 |
| upper limit | 52.3 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at LFU in the m-MITT Part A

| | |
|--|---|
| End point title | Clinical cure at LFU in the m-MITT Part A |
| End point description: | |
| A treatment difference of 13.4% (95% CI: -2.8%, 29.5%) in clinical cure at LFU was observed in the sulbactam-durlobactam + imipenem/cilastatin group (41.6% [32 of 77] of patients) compared to the colistin + imipenem/cilastatin group (28.2% [22 of 78] of patients) for the m-MITT Population in Part A. | |
| End point type | Secondary |
| End point timeframe: | |
| At late follow up (LFU) visit (> Day 21 ≤ Day 28) | |

| End point values | m-MITT - Part A - Group 1 | m-MITT - Part A -Group 2 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 | 78 | | |
| Units: patients | 32 | 22 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: | |
| Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | m-MITT - Part A -Group 2 v m-MITT - Part A - Group 1 |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 13.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | 29.5 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at LFU in the CRABC m-MITT Part A

| | |
|---|---|
| End point title | Clinical cure at LFU in the CRABC m-MITT Part A |
| End point description: | |
| A treatment difference of 12.2% (95% CI: -6.2%, 30.6%) in clinical cure at LFU was observed in the sulbactam-durlobactam + imipenem/cilastatin group (42.9% [27 of 63] of patients) compared to the colistin + imipenem/cilastatin group (30.6% [19 of 62] of patients) for the CRABC m-MITT Population, excluding patients who withdrew consent. | |
| End point type | Secondary |
| End point timeframe: | |
| At late follow up (LFU) visit (> Day 21 ≤ Day 28) | |

| End point values | CRABC m-MITT Population in Part A-Group 1 | CRABC m-MITT Population in Part A-Group 2 | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 63 | 62 | | |
| Units: patients | 27 | 19 | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|---|---|
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | CRABC m-MITT Population in Part A-Group 1 v CRABC m-MITT Population in Part A-Group 2 |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 12.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.2 |
| upper limit | 30.6 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at LFU in the CE Part A

| | |
|--|---------------------------------------|
| End point title | Clinical cure at LFU in the CE Part A |
| End point description: A treatment difference of 10.5% (95% CI: -8.0%, 29.1%) in clinical cure at LFU was observed in the sulbactam-durlobactam + imipenem/cilastatin group (43.3% [29 of 67] of patients) compared to the colistin + imipenem/cilastatin group (32.8% [19 of 58] of patients) for the CE Population in Part A. | |
| End point type | Secondary |
| End point timeframe: At late follow up (LFU) visit (> Day 21 ≤ Day 28) | |

| End point values | CE Population - Part A - Group 1 | CE Population - Part A - Group 2 | | |
|-----------------------------|----------------------------------|----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 67 | 58 | | |
| Units: patients | 29 | 19 | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|---|---|
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | CE Population - Part A - Group 1 v CE Population - Part A - Group 2 |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 10.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8 |
| upper limit | 29.1 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at LFU in the ME Part A

| | |
|------------------------|--|
| End point title | Clinical cure at LFU in the ME Part A |
| End point description: | A treatment difference of 8.0% (95% CI: -11.9%, 28.0%) in clinical cure at LFU was observed in the sulbactam-durlobactam + imipenem/cilastatin group (41.4% [24 of 58] of patients) compared to the colistin + imipenem/cilastatin group (33.3% [17 of 51] of patients) for the ME Population in Part A. |
| End point type | Secondary |
| End point timeframe: | At late follow up (LFU) visit ($> \text{Day } 21 \leq \text{Day } 28$) |

| End point values | ME Population - Part A -Group 1 | ME Population - Part A -Group 2 | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 58 | 51 | | |
| Units: patients | 24 | 17 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: | Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. |
| Comparison groups | ME Population - Part A -Group 2 v ME Population - Part A - Group 1 |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 8 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.9 |
| upper limit | 28 |
| Variability estimate | Standard deviation |

Secondary: Clinical cure at LFU in the CRABC ME Part A

| | |
|--|---|
| End point title | Clinical cure at LFU in the CRABC ME Part A |
| End point description: A treatment difference of 9.5% (95% CI: -12.5%, 31.5%) in clinical cure at LFU was observed in the sulbactam-durlobactam + imipenem/cilastatin group (41.3% [19 of 46] of patients) compared to the colistin + imipenem/cilastatin group (31.8% [14 of 44] of patients) for the CRABC ME Population in Part A. | |
| End point type | Secondary |
| End point timeframe: At late follow up (LFU) visit (> Day 21 ≤ Day 28) | |

| End point values | CRABC ME Population - Part A - Group 1 | CRABC ME Population - Part A - Group 2 | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 46 | 44 | | |
| Units: patients | 19 | 14 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | CRABC ME Population - Part A - Group 1 v CRABC ME Population - Part A - Group 2 |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 9.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.5 |
| upper limit | 31.5 |

| | |
|----------------------|--------------------|
| Variability estimate | Standard deviation |
|----------------------|--------------------|

Secondary: Microbiological (overall) favorable assessment at EOT in the CRABC m-MITT population Part A

| | |
|--|---|
| End point title | Microbiological (overall) favorable assessment at EOT in the CRABC m-MITT population Part A |
| End point description: Overall, a significant treatment difference of 24.4% (95% CI: 7.9%, 40.9%) in microbiological favorable assessment at EOT was observed with 85.7% (54 of 63) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 61.3% (38 of 62) of patients in the colistin + imipenem/cilastatin group for the CRABC m-MITT Population, excluding patients who withdrew consent. | |
| End point type | Secondary |
| End point timeframe: At end of treatment (EOT) visit (\geq Day 7 \leq Day 14) | |

| End point values | CRABC m-MITT Population in Part A-Group 1 | CRABC m-MITT Population in Part A-Group 2 | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 63 | 62 | | |
| Units: patients | 54 | 38 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | CRABC m-MITT Population in Part A-Group 1 v CRABC m-MITT Population in Part A-Group 2 |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 24.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.9 |
| upper limit | 40.9 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at TOC in the CRABC m-MITT population Part A

| | |
|-----------------|---|
| End point title | Microbiological (overall) favorable assessment at TOC in the CRABC m-MITT population Part A |
|-----------------|---|

End point description:

Overall, a significant treatment difference of 26.3% (95% CI: 7.9%, 44.7%) in microbiological favorable assessment at TOC was observed with 68.3% (43 of 63) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 41.9% (26 of 62) of patients in the colistin + imipenem/cilastatin group for the CRABC m-MITT Population, excluding patients who withdrew consent.

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

End point timeframe:

The Test of Cure (TOC) Visit was completed 7 days (± 2 days) after the EOT Visit for all patients

| End point values | CRABC m-MITT Population in Part A-Group 1 | CRABC m-MITT Population in Part A-Group 2 | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 63 | 62 | | |
| Units: patients | 43 | 26 | | |

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Treatment Difference |
|----------------------------|----------------------|

Statistical analysis description:

Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic.

| | |
|---|---|
| Comparison groups | CRABC m-MITT Population in Part A-Group 1 v CRABC m-MITT Population in Part A-Group 2 |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 26.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.9 |
| upper limit | 44.7 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at LFU in the CRABC m-MITT population Part A

| | |
|-----------------|---|
| End point title | Microbiological (overall) favorable assessment at LFU in the CRABC m-MITT population Part A |
|-----------------|---|

End point description:

A treatment difference of 7.3% (95% CI: -11.7%, 26.3%) in microbiological favorable assessment at LFU was observed in the sulbactam-durlobactam + imipenem/cilastatin group (47.6% [30 of 63] of patients) compared to the colistin + imipenem/cilastatin group (40.3% [25 of 62] of patients) for the CRABC m-MITT Population, excluding patients who withdrew consent.

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

End point timeframe:

At late follow up (LFU) visit (> Day 21 ≤ Day 28)

| End point values | CRABC m-MITT Population in Part A-Group 1 | CRABC m-MITT Population in Part A-Group 2 | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 63 | 62 | | |
| Units: patients | 30 | 25 | | |

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Treatment Difference |
|----------------------------|----------------------|

Statistical analysis description:

Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic.

| | |
|---|---|
| Comparison groups | CRABC m-MITT Population in Part A-Group 1 v CRABC m-MITT Population in Part A-Group 2 |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 7.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.7 |
| upper limit | 26.3 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at EOT in the m-MITT population Part A

| | |
|-----------------|---|
| End point title | Microbiological (overall) favorable assessment at EOT in the m-MITT population Part A |
|-----------------|---|

End point description:

A significant treatment difference of 21.6% (95% CI: 6.6%, 36.5%) in microbiological favorable assessment at EOT was observed with 83.1% (64 of 77) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 61.5% (48 of 78) of patients in the colistin + imipenem/cilastatin group for the m-MITT Population

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

End point timeframe:

At end of treatment (EOT) visit (\geq Day 7 \leq Day 14)

| End point values | m-MITT - Part A - Group 1 | m-MITT - Part A -Group 2 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 | 78 | | |
| Units: patients | 64 | 48 | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|----------------------------|----------------------|
|----------------------------|----------------------|

Statistical analysis description:

Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic.

| | |
|---|--|
| Comparison groups | m-MITT - Part A - Group 1 v m-MITT - Part A -Group 2 |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 21.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.6 |
| upper limit | 36.5 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at TOC in the m-MITT population Part A

| | |
|-----------------|---|
| End point title | Microbiological (overall) favorable assessment at TOC in the m-MITT population Part A |
|-----------------|---|

End point description:

A significant treatment difference of 25.2% (95% CI: 8.7%, 41.7%) in microbiological favorable assessment at TOC was observed with 66.2% (51 of 77) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 41.0% (32 of 78) of patients in the colistin + imipenem/cilastatin group for the m-MITT Population

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

End point timeframe:

The Test of Cure (TOC) Visit was completed 7 days (± 2 days) after the EOT Visit for all patients.

| End point values | m-MITT - Part A - Group 1 | m-MITT - Part A -Group 2 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 | 78 | | |
| Units: patients | 51 | 32 | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|---|--|
| Statistical analysis description: | |
| Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | m-MITT - Part A - Group 1 v m-MITT - Part A -Group 2 |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 25.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.7 |
| upper limit | 41.7 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at LFU in the m-MITT population Part A

| End point title | Microbiological (overall) favorable assessment at LFU in the m-MITT population Part A |
|---|---|
| End point description: | |
| A treatment difference (9.6% [95% CI: -7.2%, 26.4%]) in microbiological favorable assessment at LFU was observed with 48.1% (37 of 77) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 38.5% (30 of 78) of patients in the colistin + imipenem/cilastatin group for the m-MITT Population. | |
| End point type | Secondary |
| End point timeframe: | |
| At late follow up (LFU) visit (> Day 21 ≤ Day 28) | |

| End point values | m-MITT - Part A - Group 1 | m-MITT - Part A -Group 2 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 | 78 | | |
| Units: patients | 37 | 30 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | m-MITT - Part A - Group 1 v m-MITT - Part A -Group 2 |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 9.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.2 |
| upper limit | 26.4 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at EOT in the ME population Part A

| | |
|--|---|
| End point title | Microbiological (overall) favorable assessment at EOT in the ME population Part A |
| End point description: A significant treatment difference of 20.0% (95% CI: 1.7%, 38.3%) in microbiological favorable assessment at EOT was observed with 82.8% (48 of 58) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 62.7% (32 of 51) of patients in the colistin + imipenem/cilastatin group for the ME Population. | |
| End point type | Secondary |
| End point timeframe: At end of treatment (EOT) visit (\geq Day 7 \leq Day 14) | |

| End point values | ME Population - Part A -Group 1 | ME Population - Part A -Group 2 | | |
|-----------------------------|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 58 | 51 | | |
| Units: patients | 48 | 32 | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|--|--|
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | ME Population - Part A -Group 1 v ME Population - Part A - Group 2 |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 20 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.7 |
| upper limit | 38.3 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at TOC in the ME population Part A

| | |
|---|---|
| End point title | Microbiological (overall) favorable assessment at TOC in the ME population Part A |
| End point description: A significant treatment difference of 26.1% (95% CI: 6.1%, 46.0%) in microbiological favorable assessment at TOC was observed with 67.2% (39 of 58) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 41.2% (21 of 51) of patients in the colistin + imipenem/cilastatin group for the ME Population | |
| End point type | Secondary |
| End point timeframe: The Test of Cure (TOC) Visit was completed 7 days (±2 days) after the EOT Visit for all patients. | |

| End point values | ME Population - Part A -Group 1 | ME Population - Part A -Group 2 | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 58 | 51 | | |
| Units: patients | 39 | 21 | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|--|----------------------|
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |

| | |
|---|--|
| Comparison groups | ME Population - Part A -Group 1 v ME Population - Part A - Group 2 |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 26.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.1 |
| upper limit | 46 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at LFU in the ME population Part A

| | |
|---|---|
| End point title | Microbiological (overall) favorable assessment at LFU in the ME population Part A |
| End point description: A treatment difference (7.1% [95% CI: -13.4%, 27.6%]) in microbiological favorable assessment at LFU was observed with 48.3% (28 of 58) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 41.2% (21 of 51) of patients in the colistin + imipenem/cilastatin group for the ME Population | |
| End point type | Secondary |
| End point timeframe: At late follow up (LFU) visit (> Day 21 ≤ Day 28) | |

| End point values | ME Population - Part A -Group 1 | ME Population - Part A -Group 2 | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 58 | 51 | | |
| Units: patients | 28 | 21 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. | |
| Comparison groups | ME Population - Part A -Group 2 v ME Population - Part A - Group 1 |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 7.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.4 |
| upper limit | 27.6 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at EOT in the CRABC ME population Part A

| | |
|---|---|
| End point title | Microbiological (overall) favorable assessment at EOT in the CRABC ME population Part A |
| End point description: | |
| A treatment difference (19.0% [95% CI: -1.2%, 39.1%]) in microbiological favorable assessment at EOT was observed with 82.6% (38 of 46) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 63.6% (28 of 44) of patients in the colistin + imipenem/cilastatin group for the CRABC ME Population | |
| End point type | Secondary |
| End point timeframe: | |
| At end of treatment (EOT) visit (\geq Day 7 \leq Day 14) | |

| End point values | CRABC ME Population - Part A - Group 1 | CRABC ME Population - Part A - Group 2 | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 46 | 44 | | |
| Units: patients | 38 | 28 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: | |
| Summarized by treatment group. Two-sided 95% CIs computed using a continuity-corrected Z-statistic for the difference in outcome rates between the treatment groups in Part A. | |
| Comparison groups | CRABC ME Population - Part A - Group 1 v CRABC ME Population - Part A - Group 2 |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 39.1 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at TOC in the CRABC ME population Part A

| | |
|------------------------|---|
| End point title | Microbiological (overall) favorable assessment at TOC in the CRABC ME population Part A |
| End point description: | A significant treatment difference of 28.7% (95% CI: 6.7%, 50.6%) in microbiological favorable assessment at TOC was observed with 69.6% (32 of 46) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 40.9% (18 of 44) of patients in the colistin + imipenem/cilastatin group for the CRABC ME Population |
| End point type | Secondary |
| End point timeframe: | The Test of Cure (TOC) Visit was completed 7 days (± 2 days) after the EOT Visit for all patients |

| End point values | CRABC ME Population - Part A - Group 1 | CRABC ME Population - Part A - Group 2 | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 46 | 44 | | |
| Units: patients | 32 | 18 | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: | Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. |
| Comparison groups | CRABC ME Population - Part A - Group 1 v CRABC ME Population - Part A - Group 2 |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 28.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.7 |
| upper limit | 50.6 |
| Variability estimate | Standard deviation |

Secondary: Microbiological (overall) favorable assessment at LFU in the CRABC ME population Part A

| | |
|------------------------|---|
| End point title | Microbiological (overall) favorable assessment at LFU in the CRABC ME population Part A |
| End point description: | A treatment difference (6.9% [95% CI: -15.8%, 29.6%]) in microbiological favorable assessment at LFU was observed with 47.8% (22 of 46) of patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to 40.9% (18 of 44) of patients in the colistin + imipenem/cilastatin group for the CRABC ME Population |
| End point type | Secondary |
| End point timeframe: | At late follow up (LFU) visit (> Day 21 ≤ Day 28) |

| End point values | CRABC ME Population - Part A - Group 1 | CRABC ME Population - Part A - Group 2 | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 46 | 44 | | |
| Units: patients | 22 | 18 | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: | Treatment difference was the difference in the clinical cure rate between the 2 treatment arms([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. |
| Comparison groups | CRABC ME Population - Part A - Group 1 v CRABC ME Population - Part A - Group 2 |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | 6.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.8 |
| upper limit | 29.6 |
| Variability estimate | Standard deviation |

Secondary: 14-day all-cause mortality in the m-MITT Populations

| | |
|--|--|
| End point title | 14-day all-cause mortality in the m-MITT Populations |
| End point description: | |
| Sulbactam-durlobactam + imipenem/cilastatin met the secondary efficacy endpoint of 14-day all-cause mortality compared to colistin + imipenem/cilastatin in the m-MITT Population for Part A. The 14-day all-cause mortality rate in the sulbactam-durlobactam + imipenem/cilastatin group was 7.8% (6 of 77 patients) compared to 19.5% (15 of 77 patients) in the colistin + imipenem/cilastatin group (treatment difference of -11.7%; 95% CI: -23.7%, 0.3%) for the m-MITT Population. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 14 | |

| End point values | m-MITT - Part A - Group 1 | m-MITT - Part A -Group 2 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 | 77 | | |
| Units: patients | 6 | 15 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: | |
| Summarized by treatment group. Two-sided 95% CIs computed using a continuity-corrected Z-statistic for the difference in outcome rates between the treatment groups in Part A. | |
| Comparison groups | m-MITT - Part A - Group 1 v m-MITT - Part A -Group 2 |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | -11.7 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.7 |
| upper limit | 0.3 |
| Variability estimate | Standard deviation |

Secondary: 14-day all-cause mortality in the CRABC m-MITT Population

| | |
|--|---|
| End point title | 14-day all-cause mortality in the CRABC m-MITT Population |
| End point description: | |
| Treatment differences in 14-day all-cause mortality were observed for patients in the sulbactam-durlobactam + imipenem/cilastatin group compared to the imipenem/cilastatin group. The treatment difference between the 2 groups was -12.8% (95% CI: -25.7%, 0.1%). The mortality rate in the sulbactam-durlobactam + imipenem/cilastatin group was 6.3% (4 of 64 patients) compared to 19.0% (12 of 63 patients) in the colistin + imipenem/cilastatin group for the CRABC m-MITT Population. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 14 | |

| End point values | CRABC m-MITT Population in Part A-Group 1 | CRABC m-MITT Population in Part A-Group 2 | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 64 | 63 | | |
| Units: patients | 4 | 12 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: | |
| Summarized by treatment group. Two-sided 95% CIs computed using a continuity-corrected Z-statistic for the difference in outcome rates between the treatment groups in Part A. | |
| Comparison groups | CRABC m-MITT Population in Part A-Group 2 v CRABC m-MITT Population in Part A-Group 1 |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | -12.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.7 |
| upper limit | 0.1 |

| | |
|----------------------|--------------------|
| Variability estimate | Standard deviation |
|----------------------|--------------------|

Secondary: 28-day all-cause mortality in the m-MITT Population

| | |
|--|---|
| End point title | 28-day all-cause mortality in the m-MITT Population |
| End point description: The 28-day all-cause mortality rate in the sulbactam-durlobactam + imipenem/cilastatin group was 19.7% (15 of 76 patients) compared to 32.9% (25 of 76 patients) in the colistin + imipenem/cilastatin group (treatment difference of -13.2%; 95% CI: -28.3%, 2.0%) for the m-MITT Population. | |
| End point type | Secondary |
| End point timeframe: Day 28 | |

| End point values | m-MITT - Part A - Group 1 | m-MITT - Part A -Group 2 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 76 | 76 | | |
| Units: patients | 15 | 25 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: Summarized by treatment group. Two-sided 95% CIs computed using a continuity-corrected Z-statistic for the difference in outcome rates between the treatment groups in Part A. | |
| Comparison groups | m-MITT - Part A - Group 1 v m-MITT - Part A -Group 2 |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | -13.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -28.3 |
| upper limit | 2 |
| Variability estimate | Standard deviation |

Secondary: 28-day all-cause mortality in the CRABC ME Population

| | |
|---|---|
| End point title | 28-day all-cause mortality in the CRABC ME Population |
| End point description: The 28-day all-cause mortality rate in the sulbactam-durlobactam + imipenem/cilastatin group was 17.4% (8 of 46 patients) compared to 36.4% (16 of 44 patients) in the colistin + imipenem/cilastatin | |

group (treatment difference of -19.0%; 95% CI: -39.1%, 1.2%) for the CRABC ME Population, which represents a Clinical Study Protocol-adherent population.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 28 | |

| End point values | CRABC ME Population - Part A - Group 1 | CRABC ME Population - Part A - Group 2 | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 46 | 44 | | |
| Units: patients | 8 | 16 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Treatment Difference |
| Statistical analysis description: | |
| Summarized by treatment group. Two-sided 95% CIs computed using a continuity-corrected Z-statistic for the difference in outcome rates between the treatment groups in Part A. | |
| Comparison groups | CRABC ME Population - Part A - Group 1 v CRABC ME Population - Part A - Group 2 |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (net) |
| Point estimate | -19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -39.1 |
| upper limit | 1.2 |
| Variability estimate | Standard deviation |

Secondary: 28-day all-cause mortality in the ITT Population - Part B

| | |
|---|--|
| End point title | 28-day all-cause mortality in the ITT Population - Part B ^[5] |
| End point description: | |
| For Part B, 28-day all-cause mortality was 17.9% (5 of 28 patients) (95% CI: 6.1%, 36.9%) for the ITT Population. | |
| The Part B 28-day all-cause mortality was similar to the sulbactam-durlobactam + imipenem/cilastatin group in Part A for the CRABC m-MITT Population (17.9% and 20.3%, respectively). | |
| End point type | Secondary |
| End point timeframe: | |
| Day 28 | |

Notes:

[5] - 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: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at TOC in the CRABC m-MITT Population - Part B

| | |
|-----------------|---|
| End point title | Clinical cure at TOC in the CRABC m-MITT Population - Part B ^[6] |
|-----------------|---|

End point description:

For Part B, clinical cure at TOC was observed with 71.4% (20 of 28) of patients for the CRABC m-MITT Population.

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

End point timeframe:

The Test of Cure (TOC) Visit was completed 7 days (± 2 days) after the EOT Visit for all patients

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 20 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at TOC in the m-MITT Population - Part B

| | |
|-----------------|---|
| End point title | Clinical cure at TOC in the m-MITT Population - Part B ^[7] |
|-----------------|---|

End point description:

For Part B, clinical cure at TOC was observed with 71.4% (20 of 28) of patients for the m-MITT Population.

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

End point timeframe:

The Test of Cure (TOC) Visit was completed 7 days (± 2 days) after the EOT Visit for all patients

Notes:

[7] - 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: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 20 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at TOC in the CE, ME, and CRABC ME Population - Part B

| | |
|-----------------|---|
| End point title | Clinical cure at TOC in the CE, ME, and CRABC ME Population - Part B ^[8] |
|-----------------|---|

End point description:

For Part B, clinical cure at TOC was observed with 78.3% (18 of 23) of patients each for the CE, ME, and CRABC ME Populations.

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

End point timeframe:

The Test of Cure (TOC) Visit was completed 7 days (± 2 days) after the EOT Visit for all patients

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: patients | 18 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at EOT in the CRABC m-MITT Population -Part B

| | |
|-----------------|--|
| End point title | Clinical cure at EOT in the CRABC m-MITT Population -Part B ^[9] |
|-----------------|--|

End point description:

For Part B, clinical cure at EOT was observed with 82.1% (23 of 28) of patients for the CRABC m-MITT Population.

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

End point timeframe:

At end of treatment (EOT) visit (\geq Day 7 \leq Day 14)

Notes:

[9] - 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: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 23 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at LFU in the CRABC m-MITT Population -Part B

| | |
|-----------------|---|
| End point title | Clinical cure at LFU in the CRABC m-MITT Population -Part B ^[10] |
|-----------------|---|

End point description:

For Part B, clinical cure at LFU was observed with 46.4% (13 of 28) of patients for the CRABC m-MITT Population

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

End point timeframe:

At late follow up (LFU) visit ($> \text{Day } 21 \leq \text{Day } 28$)

Notes:

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

Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 13 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at EOT in the m-MITT Population -Part B

| | |
|-----------------|---|
| End point title | Clinical cure at EOT in the m-MITT Population -Part B ^[11] |
|-----------------|---|

End point description:

For Part B, clinical cure at EOT was observed with 82.1% (23 of 28) of patients for the m-MITT Population.

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

End point timeframe:

At end of treatment (EOT) visit ($\geq \text{Day } 7 \leq \text{Day } 14$)

Notes:

[11] - 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: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 23 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at LFU in the m-MITT Population -Part B

| | |
|--|---|
| End point title | Clinical cure at LFU in the m-MITT Population -Part B ^[12] |
| End point description: For Part B, clinical cure at LFU was observed with 46.4% (13 of 28) of patients for the m-MITT Population. | |
| End point type | Secondary |
| End point timeframe: At late follow up (LFU) visit (> Day 21 ≤ Day 28) | |

Notes:

[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: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 13 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at EOT in the CE, ME and CRABC ME Populations -Part B

| | |
|--|--|
| End point title | Clinical cure at EOT in the CE, ME and CRABC ME Populations - Part B ^[13] |
| End point description: For Part B, clinical cure at EOT was observed with 82.6% (19 of 23) of patients for the CE, ME and CRABC ME populations. | |
| End point type | Secondary |

End point timeframe:

At end of treatment (EOT) visit (\geq Day 7 \leq Day 14)

Notes:

[13] - 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: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: patients | 19 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at LFU in the CE, ME and CRABC ME Populations -Part B

| | |
|-----------------|--|
| End point title | Clinical cure at LFU in the CE, ME and CRABC ME Populations - Part B ^[14] |
|-----------------|--|

End point description:

For Part B, clinical cure at LFU was observed with 52.2% (12 of 23) of patients for the CE, ME and CRABC ME populations.

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

End point timeframe:

At late follow up (LFU) visit ($>$ Day 21 \leq Day 28)

Notes:

[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: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: patients | 12 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological (overall) favorable assessment at EOT in the m-MITT and CRABC m-MITT population - Part B

| | |
|-----------------|--|
| End point title | Microbiological (overall) favorable assessment at EOT in the m-MITT and CRABC m-MITT population - Part B ^[15] |
|-----------------|--|

End point description:

Overall, microbiological favorable assessment at EOT was observed with 89.3% (25 of 28) of patients

for the CRABC m-MITT Population.

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

End point timeframe:

At end of treatment (EOT) visit (\geq Day 7 \leq Day 14)

Notes:

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

Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 25 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological (overall) favorable assessment at LFU in the m-MITT and CRABC m-MITT population - Part B

| | |
|-----------------|--|
| End point title | Microbiological (overall) favorable assessment at LFU in the m-MITT and CRABC m-MITT population - Part B ^[16] |
|-----------------|--|

End point description:

Overall, microbiological favorable assessment at LFU was observed with 53.6% (15 of 28) of patients.

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

End point timeframe:

At late follow up (LFU) visit ($>$ Day 21 \leq Day 28)

Notes:

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

Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 15 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological (overall) favorable assessment at TOC in the m-MITT and CRABC m-MITT population - Part B

| | |
|-----------------|---|
| End point title | Microbiological (overall) favorable assessment at TOC in the m- |
|-----------------|---|

End point description:

Overall, microbiological favorable assessment at TOC was observed with 78.6% (22 of 28) of patients

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

End point timeframe:

The Test of Cure (TOC) Visit was completed 7 days (± 2 days) after the EOT Visit for all patients.

Notes:

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

Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| End point values | Part B - Group 3 | | | |
|-----------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 22 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological (overall) favorable assessment at EOT in the ME and CRABC ME populations – Part B

| | |
|-----------------|---|
| End point title | Microbiological (overall) favorable assessment at EOT in the ME and CRABC ME populations – Part B ^[18] |
|-----------------|---|

End point description:

Overall, microbiological favorable assessment at EOT was observed with 95.7% (22 of 23) of patients for the ME and CRABC ME populations.

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

End point timeframe:

At end of treatment (EOT) visit (\geq Day 7 \leq Day 14)

Notes:

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

Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| End point values | Part B - Group 3 | | | |
|-----------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: patients | 22 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological (overall) favorable assessment at TOC in the ME and CRABC ME populations – Part B

| | |
|-----------------|---|
| End point title | Microbiological (overall) favorable assessment at TOC in the ME and CRABC ME populations – Part B ^[19] |
|-----------------|---|

End point description:

Overall, microbiological favorable assessment at TOC was observed with 87.0% (20 of 23) of patients for the ME and CRABC ME populations.

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

End point timeframe:

The Test of Cure (TOC) Visit was completed 7 days (± 2 days) after the EOT Visit for all patients.

Notes:

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

Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: patients | 20 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological (overall) favorable assessment at LFU in the ME and CRABC ME populations – Part B

| | |
|-----------------|---|
| End point title | Microbiological (overall) favorable assessment at LFU in the ME and CRABC ME populations – Part B ^[20] |
|-----------------|---|

End point description:

Overall, microbiological favorable assessment at LFU was observed with 60.9% (14 of 23) of patients for the ME and CRABC ME populations.

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

End point timeframe:

At late follow up (LFU) visit ($> \text{Day } 21 \leq \text{Day } 28$)

Notes:

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

Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: patients | 14 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 14-day all-cause mortality in the CRABC m-MITT and m-MITT Populations - Part B

| | |
|-----------------|--|
| End point title | 14-day all-cause mortality in the CRABC m-MITT and m-MITT Populations - Part B ^[21] |
|-----------------|--|

End point description:

For Part B, 14-day all-cause mortality was 10.7% (3 of 28) of patients each (95% CI: 2.3%, 28.2%) for both the m-MITT and CRABC m-MITT Populations.

The Part B 14-day all-cause mortality was similar to the sulbactam-durlobactam + imipenem/cilastatin group in Part A for the CRABC m-MITT Population (10.7% and 6.3%, respectively).

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

End point timeframe:

Day 14

Notes:

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

Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 28-day all-cause mortality in the m-MITT Population - Part B

| | |
|-----------------|--|
| End point title | 28-day all-cause mortality in the m-MITT Population - Part B ^[22] |
|-----------------|--|

End point description:

For Part B, 28-day all-cause mortality was 17.9% (5 of 28) of patients (95% CI: 6.1%, 36.9%) for the m-MITT Population.

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

End point timeframe:

Day 28

Notes:

[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: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: patients | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 28-day all-cause mortality in the CRABC ME Population - Part B

| | |
|-----------------|--|
| End point title | 28-day all-cause mortality in the CRABC ME Population - Part |
|-----------------|--|

End point description:

For Part B, 28-day all-cause mortality was 8.7% (2 of 23) of patients (95% CI: 1.1%, 28.0%) for the CRABC ME Population.

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

End point timeframe:

Day 28

Notes:

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

Justification: Even if all 3 arms, Part A (Group 1 and 2) and Part B (Group 3) are all part of the baseline period, Part B data was summarized separately from Part A using descriptive statistics.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Part B - Group 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: patients | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event monitoring starts from the time the patient consents to the study until they complete the trial.

Adverse event reporting additional description:

A Treatment-emergent adverse event (TEAE) was defined as an adverse event (AE) that occurred on or after the administration of the first dose of study drug.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Safety Population- Part A - Group 1 - experimental group |
|-----------------------|--|

Reporting group description:

In total, 91 patients received any amount of study drug treatment in Part A - Group 1 and were considered the Safety Population for this group.

| | |
|-----------------------|--|
| Reporting group title | Safety Population-Part A - Group 2 - control group |
|-----------------------|--|

Reporting group description:

In total, 86 patients received any amount of study drug treatment in Part A - Group 2 - control group and were considered the Safety Population for this group.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Safety Population-Part B - Group 3 |
|-----------------------|------------------------------------|

Reporting group description:

There were 28 patients who received any amount of study drug in Part B and were included in the Safety Population for Part B.

| Serious adverse events | Safety Population- Part A - Group 1 - experimental group | Safety Population- Part A - Group 2 - control group | Safety Population- Part B - Group 3 |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 36 / 91 (39.56%) | 42 / 86 (48.84%) | 9 / 28 (32.14%) |
| number of deaths (all causes) | 25 | 31 | 4 |
| number of deaths resulting from adverse events | 24 | 30 | 4 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Metastases to central nervous system | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Shock | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 4 / 86 (4.65%) | 2 / 28 (7.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 2 |
| Disease progression | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercapnia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Tracheomalacia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Chemical peritonitis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheostomy malfunction | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weaning failure | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Congenital, familial and genetic disorders | | | |
| Tracheo-oesophageal fistula | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 4 / 86 (4.65%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|----------------|----------------|----------------|
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Agranulocytosis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Neutropenia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer perforation | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intra-abdominal haemorrhage | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Thrombosis mesenteric vessel | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic hepatitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Primary biliary cholangitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |

| | | | |
|---|----------------|----------------|----------------|
| Septic shock | | | |
| subjects affected / exposed | 7 / 91 (7.69%) | 7 / 86 (8.14%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 5 | 0 / 5 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 4 / 86 (4.65%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 4 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| Acinetobacter infection | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronavirus infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mastoiditis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis bacterial | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomembranous colitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic candida | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

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

| Non-serious adverse events | Safety Population- Part A - Group 1 - experimental group | Safety Population- Part A - Group 2 - control group | Safety Population- Part B - Group 3 |
|--|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 76 / 91 (83.52%) | 78 / 86 (90.70%) | 23 / 28 (82.14%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Meningioma | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|----------------|----------------|----------------|
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 91 (5.49%) | 5 / 86 (5.81%) | 1 / 28 (3.57%) |
| occurrences (all) | 5 | 5 | 1 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 1 / 28 (3.57%) |
| occurrences (all) | 2 | 1 | 1 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 1 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Shock | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Blood pressure inadequately controlled | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Brachiocephalic vein thrombosis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Distributive shock | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoperfusion | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Peripheral artery occlusion | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 9 / 91 (9.89%) | 8 / 86 (9.30%) | 1 / 28 (3.57%) |
| occurrences (all) | 14 | 11 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 9 | 1 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Catheter site inflammation | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Catheter site injury | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypothermia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Localised oedema | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hydrothorax | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 4 | 0 | 1 |
| Respiratory acidosis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Atelectasis | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 3 | 0 | 1 |
| Pulmonary oedema | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 1 / 28 (3.57%) |
| occurrences (all) | 2 | 1 | 1 |
| Wheezing | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Bronchial obstruction | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 2 | 0 | 1 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pleurisy | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Respiratory alkalosis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bronchitis chronic | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 0 | 1 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory distress | | | |

| | | | |
|-------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sputum decreased | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tracheal mass | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tracheal stenosis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Increased bronchial secretion | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Pharyngeal haemorrhage | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Agitation | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Delusion | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|--|---------------------|----------------------|----------------------|
| Depression subjects affected / exposed occurrences (all) | 1 / 91 (1.10%) 1 | 0 / 86 (0.00%) 0 | 0 / 28 (0.00%) 0 |
| Tic subjects affected / exposed occurrences (all) | 0 / 91 (0.00%) 0 | 0 / 86 (0.00%) 0 | 1 / 28 (3.57%) 1 |
| Investigations | | | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 2 / 91 (2.20%) 6 | 7 / 86 (8.14%) 10 | 3 / 28 (10.71%) 3 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 91 (3.30%) 4 | 2 / 86 (2.33%) 3 | 1 / 28 (3.57%) 1 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 3 / 91 (3.30%) 5 | 2 / 86 (2.33%) 2 | 1 / 28 (3.57%) 1 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 91 (3.30%) 4 | 2 / 86 (2.33%) 2 | 1 / 28 (3.57%) 1 |
| Bilirubin conjugated increased subjects affected / exposed occurrences (all) | 2 / 91 (2.20%) 5 | 1 / 86 (1.16%) 1 | 0 / 28 (0.00%) 0 |
| Electrocardiogram QT prolonged subjects affected / exposed occurrences (all) | 3 / 91 (3.30%) 3 | 1 / 86 (1.16%) 1 | 0 / 28 (0.00%) 0 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 1 / 91 (1.10%) 2 | 2 / 86 (2.33%) 2 | 2 / 28 (7.14%) 2 |
| Neutrophil count increased subjects affected / exposed occurrences (all) | 2 / 91 (2.20%) 4 | 0 / 86 (0.00%) 0 | 0 / 28 (0.00%) 0 |
| Protein urine present subjects affected / exposed occurrences (all) | 3 / 91 (3.30%) 3 | 1 / 86 (1.16%) 1 | 0 / 28 (0.00%) 0 |
| Blood albumin decreased | | | |

| | | | |
|---------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 2 / 28 (7.14%) |
| occurrences (all) | 2 | 1 | 2 |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 2 / 86 (2.33%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 2 | 1 |
| Blood urine present | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 2 / 86 (2.33%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 2 | 1 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Platelet count increased | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Staphylococcus test positive | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 2 / 86 (2.33%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 2 | 1 |
| Blood calcium decreased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood calcium increased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 1 | 1 |

| | | | |
|--|----------------|----------------|----------------|
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 2 | 0 | 1 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| QRS axis abnormal | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Albumin globulin ratio decreased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bilirubin urine present | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 2 / 28 (7.14%) |
| occurrences (all) | 0 | 1 | 2 |
| Blood chloride decreased | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood creatine phosphokinase decreased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood glucose decreased | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood lactic acid increased | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood uric acid increased | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Computerised tomogram kidney abnormal | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Creatinine renal clearance increased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Electrocardiogram high voltage | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| False positive investigation result | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mycobacterium tuberculosis complex test positive | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pseudomonas test positive | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Red blood cells urine positive | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urine ketone body present | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urobilinogen urine increased | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Enterococcus test positive | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 3 / 28 (10.71%) |
| occurrences (all) | 0 | 0 | 3 |
| Proteus test positive | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neck injury | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Post-traumatic pain | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thermal burn | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urethral injury | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Wound haemorrhage | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 91 (0.00%) 0 | 0 / 86 (0.00%) 0 | 1 / 28 (3.57%) 1 |
| Congenital, familial and genetic disorders | | | |
| Porencephaly | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tracheo-oesophageal fistula | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 4 / 86 (4.65%) | 1 / 28 (3.57%) |
| occurrences (all) | 3 | 6 | 1 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Bundle branch block left | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Aortic valve disease mixed | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 0 | 1 |
| Cardiac arrest | | | |

| | | | |
|--------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mitral valve disease mixed | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 0 | 1 |
| Pericardial mass | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Torsade de pointes | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |

| | | | |
|---------------------------------------|------------------|------------------|-----------------|
| Seizure | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Intensive care unit acquired weakness | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Neuralgia | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Polyneuropathy | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 12 / 91 (13.19%) | 10 / 86 (11.63%) | 3 / 28 (10.71%) |
| occurrences (all) | 31 | 21 | 4 |
| Leukocytosis | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 3 / 91 (3.30%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 5 / 91 (5.49%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Coagulopathy | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypofibrinogenaemia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Splenomegaly | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytosis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Conjunctival oedema | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Retinal vascular disorder | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 91 (0.00%) 0 | 1 / 86 (1.16%) 1 | 0 / 28 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 15 / 91 (16.48%) | 9 / 86 (10.47%) | 2 / 28 (7.14%) |
| occurrences (all) | 16 | 11 | 2 |
| Constipation | | | |
| subjects affected / exposed | 5 / 91 (5.49%) | 5 / 86 (5.81%) | 0 / 28 (0.00%) |
| occurrences (all) | 7 | 6 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 91 (4.40%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 5 | 3 | 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 4 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 2 / 86 (2.33%) | 2 / 28 (7.14%) |
| occurrences (all) | 0 | 3 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abdominal compartment syndrome | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Duodenogastric reflux | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysbacteriosis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastric polyps | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastroduodenal haemorrhage | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral discomfort | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Hepatobiliary disorders | | | |
| Liver injury | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 4 / 86 (4.65%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 5 | 0 |
| Hepatic failure | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 91 (1.10%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatic mass | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatitis acute | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatitis alcoholic | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 5 / 91 (5.49%) | 3 / 86 (3.49%) | 4 / 28 (14.29%) |
| occurrences (all) | 5 | 3 | 4 |
| Rash | | | |
| subjects affected / exposed | 4 / 91 (4.40%) | 2 / 86 (2.33%) | 1 / 28 (3.57%) |
| occurrences (all) | 4 | 2 | 1 |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| Dermatitis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eczema | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 9 / 86 (10.47%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 12 | 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 6 / 86 (6.98%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 9 | 1 |
| Nephropathy toxic | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 4 / 86 (4.65%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Proteinuria | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 1 / 28 (3.57%) |
| occurrences (all) | 2 | 1 | 1 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 3 / 86 (3.49%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 3 | 1 |
| Glycosuria | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Anuria | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bilirubinuria | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myoglobinuria | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neurogenic bladder | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Endocrine disorders | | | |
| Euthyroid sick syndrome | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Arthralgia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fistula | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle twitching | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 91 (7.69%) | 8 / 86 (9.30%) | 1 / 28 (3.57%) |
| occurrences (all) | 11 | 9 | 1 |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 4 / 91 (4.40%) | 2 / 86 (2.33%) | 1 / 28 (3.57%) |
| occurrences (all) | 4 | 2 | 1 |
| Septic shock | | | |

| | | | |
|--------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 91 (2.20%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Tracheobronchitis | | | |
| subjects affected / exposed | 5 / 91 (5.49%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 4 / 86 (4.65%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 4 | 1 |
| Coronavirus infection | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 91 (4.40%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Klebsiella infection | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Candida pneumonia | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Urinary tract infection fungal | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 1 / 28 (3.57%) |
| occurrences (all) | 2 | 1 | 1 |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Candidiasis of trachea | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Mastoiditis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Oropharyngeal candidiasis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pharyngitis bacterial | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Bacterial infection | | | |

| | | | |
|----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bacterial pyelonephritis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bacterial tracheitis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Burkholderia infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Central nervous system infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Enterococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fungal cystitis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Impetigo | | | |

| | | | |
|----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infected skin ulcer | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Meningitis bacterial | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myringitis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasal candidiasis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral fungal infection | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumocystis jirovecii infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia acinetobacter | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pneumonia cytomegaloviral | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Postoperative wound infection | | | |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pulmonary mucormycosis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin bacterial infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Staphylococcal skin infection | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Stenotrophomonas sepsis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Systemic mycosis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary tract infection enterococcal | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Wound abscess | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Wound infection pseudomonas | | | |

| | | | |
|------------------------------------|------------------|-----------------|----------------|
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Corynebacterium infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Enterococcal sepsis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Malaria | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Pseudomonas bronchitis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Systemic candida | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 86 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 0 | 1 |
| Lung infection pseudomonal | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Candiduria | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 13 / 91 (14.29%) | 9 / 86 (10.47%) | 0 / 28 (0.00%) |
| occurrences (all) | 21 | 19 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 5 / 86 (5.81%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 8 | 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Hypomagnesaemia | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 4 / 86 (4.65%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 6 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 4 / 86 (4.65%) | 1 / 28 (3.57%) |
| occurrences (all) | 4 | 4 | 1 |
| Hypernatraemia | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 4 / 86 (4.65%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 4 / 91 (4.40%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Hypochloraemia | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 2 / 86 (2.33%) | 0 / 28 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Hyperchloraemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 91 (3.30%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 3 / 86 (3.49%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |

| | | | |
|-----------------------------------|----------------|----------------|----------------|
| Acidosis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Metabolic alkalosis | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Alkalosis | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 86 (1.16%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 86 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 29 April 2019 | <p>Protocol Amendment 1 (version 2.0, dated 29 April 2019) was instituted before any enrollment and updated the Clinical Study Protocol in the following ways:</p> <ul style="list-style-type: none">• In response to queries from the Spanish regulatory authority, the following clarifications were made:<ul style="list-style-type: none">o Language regarding the informed consent process and use of a legally authorized representative was updated and expanded; ando Rationale was added regarding the timing of the initiation of Part B of the study, namely, that PK from Part A must be verified prior to beginning Part B. In addition, language was added to allow for patients who are responding to therapy to remain in Part A even with a colistin resistant culture.• In response to queries from the Chinese regulatory authority, intense PK sampling was conducted for the first approximately 20 patients enrolled at sites in China Mainland. Due to this change, stratification for Part A also included geography (China Mainland versus Rest of World);• Removed neutropenia requirements from diagnosis of bacteremia in Part A-specific inclusion criteria;• Language for entry into Part B was updated to allow for patients who previously failed a polymyxin-based regimen and additional clarifications were made to clarify the patient population for Part B;• Text was added to inclusion criterion 4 to clarify definition of enrollment as prior to first dose of study drug;• Removed required elevated serum lactate level from exclusion criterion 5;• Clarified that "study drug" in exclusion criterion 25 refers to durlobactam;• Language added from imipenem/cilastatin package insert to note instructions for patients who experienced focal tremors, myoclonus, or seizures at any point during the study;• Text updated throughout that, in the event of a discrepancy between the assessment of the blinded assessor and unblinded Investigator, the assessment from the blinded assessor would prevail;• Clarification added for discontinuation due to severe li |

| | |
|------------------|--|
| 14 January 2020 | <p>Protocol Amendment 2 (version 3.0, dated 14 January 2020) updated the Clinical Study Protocol in the following ways:</p> <ul style="list-style-type: none"> • The target population was expanded to allow patients with VP into Parts A and B of the study; • The following changes were made to the inclusion and exclusion criteria: <ul style="list-style-type: none"> o The definition for bacteremia was simplified; o Qualifying scores for the APACHE II and SOFA were made uniform for both Parts A and B; o Language was added allowing ultrasound for diagnosis; o Pleural fluid was added as an acceptable source for specimen collection; o Contraception language was updated based on the nonclinical study package as follows: <ul style="list-style-type: none"> -Female contraception language was updated to require only 1 highly effective method of contraception; and -Male contraception language was removed. o Acceptable comorbidities and permitted treatments were updated. • The secondary efficacy endpoint of attributable mortality was changed to all mortality; • Resistance to carbapenems was added to the exploratory efficacy endpoints; • The sample size was increased as required to allow for the interim analysis; • Language was added to clarify that an adjudication committee may be organized for endpoint adjudication; • Clarified that specimens were cultured at the local lab with pure cultures of isolates sent to the central laboratory; • Language was added to allow patients receiving antibiotic prophylaxis for immunosuppression; • The timeframe and process for retesting following an indeterminate or negative result for the BPP were defined; • Clarified the timeframe for AE collection was to begin with signing of the main informed consent, not limited scope informed consent; and • Clarified that if the first 3 of Hy's Laws were met it must be reported as an SAE. |
| 17 December 2020 | <p>Protocol Amendment 3 (version 4.0, dated 17 December 2020) updated the Clinical Study Protocol in the following ways:</p> <ul style="list-style-type: none"> • The Part B-specific inclusion criterion requiring patients to have acute kidney injury and were receiving renal replacement therapy at study entry was removed, so that patients who only met this criterion were not enrolled in Part B. Instead, this criterion was added as 1 of the potential requirements for patients with HABP, VABP, VP, or bacteremia, and for patients with cUTI, AP, or surgical or post-traumatic wound infections; • COVID-19 infection without clinical improvement was added to exclusion criteria as an example of a pulmonary disease that would preclude evaluation of a therapeutic response; • Clarification was added for the imipenem/cilastatin dose adjustments for patients with severe renal impairment; • Language of the required repeat imaging for the chest X-ray, MRI, CT scan, or ultrasound obtained >48 hours prior to randomization, was updated to avoid confusion at study sites; • Language was updated to clarify that an ABC positive culture collected within 72 hours prior to randomization rather than screening, was acceptable for enrollment; • Mortality in the CRABC m-MITT Population was removed from the secondary efficacy endpoints since the primary efficacy endpoint for the study was 28-day all-cause mortality in the CRABC m-MITT Population in Part A; • The definition of clinical indeterminate was updated; • Language was added to clarify that the local laboratory could be used to confirm if the baseline ABC organism was carbapenem resistant when the central laboratory was not able to characterize the isolate for any reason; • Additional requirements for the exclusion of patients from the CRABC m-MITT Population were added; • After the conversation with the Food and Drug Administration (FDA) (reference ID: 4667476), the non-inferiority margin was increased, and as a result, the total sample size for Part A and the sam |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported