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	• 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.

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

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
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
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 ≥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 ≥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 (≥ Day 7 ≤ 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 (≥ Day 7 ≤ 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 (≥ Day 7 ≤ 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 (≥ Day 7 ≤ 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 (≥ Day 7 ≤ 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 (> 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	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 (≥ Day 7 ≤ 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 (≥ Day 7 ≤ 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 (≥ Day 7 ≤ 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 (≥ Day 7 ≤ 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 (≥ Day 7 ≤ 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 (> Day 21 ≤ 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 (≥ Day 7 ≤ 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 (≥ Day 7 ≤ 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 ≤ 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 (≥ Day 7 ≤ 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 ≤ 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-

	MITT and CRABC m-MITT population - Part B[17]

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 (≥ Day 7 ≤ 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 (> Day 21 ≤ 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	1 / 91 (1.10%)	0 / 86 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Tic			
subjects affected / exposed	0 / 91 (0.00%)	0 / 86 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 91 (2.20%)	7 / 86 (8.14%)	3 / 28 (10.71%)
occurrences (all)	6	10	3
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 91 (3.30%)	2 / 86 (2.33%)	1 / 28 (3.57%)
occurrences (all)	4	3	1
Blood bilirubin increased			
subjects affected / exposed	3 / 91 (3.30%)	2 / 86 (2.33%)	1 / 28 (3.57%)
occurrences (all)	5	2	1
Alanine aminotransferase increased			
subjects affected / exposed	3 / 91 (3.30%)	2 / 86 (2.33%)	1 / 28 (3.57%)
occurrences (all)	4	2	1
Bilirubin conjugated increased			
subjects affected / exposed	2 / 91 (2.20%)	1 / 86 (1.16%)	0 / 28 (0.00%)
occurrences (all)	5	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 91 (3.30%)	1 / 86 (1.16%)	0 / 28 (0.00%)
occurrences (all)	3	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 91 (1.10%)	2 / 86 (2.33%)	2 / 28 (7.14%)
occurrences (all)	2	2	2
Neutrophil count increased			
subjects affected / exposed	2 / 91 (2.20%)	0 / 86 (0.00%)	0 / 28 (0.00%)
occurrences (all)	4	0	0
Protein urine present			
subjects affected / exposed	3 / 91 (3.30%)	1 / 86 (1.16%)	0 / 28 (0.00%)
occurrences (all)	3	1	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	0 / 91 (0.00%)	0 / 86 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	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	0 / 91 (0.00%)	1 / 86 (1.16%)	0 / 28 (0.00%)
occurrences (all)	0	1	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	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: • In response to queries from the Spanish regulatory authority, the following clarifications were made: o Language regarding the informed consent process and use of a legally authorized representative was updated and expanded; and o 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	Protocol Amendment 2 (version 3.0, dated 14 January 2020) updated the Clinical Study Protocol in the following ways: • 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: 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: -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	Protocol Amendment 3 (version 4.0, dated 17 December 2020) updated the Clinical Study Protocol in the following ways: • 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