Clinical trial results:
A Phase 2 Proof-of-concept Study to Evaluate the Efficacy and Safety of MEDI3902 in Mechanically Ventilated Patients for the Prevention of Nosocomial Pneumonia Caused by Pseudomonas aeruginosa

Summary

EudraCT number	2015-001706-34
Trial protocol	ES CZ HU DE BE GR PT HR AT SK
Global end of trial date	04 December 2019

Results information

Result version number	v1
This version publication date	20 November 2020
First version publication date	20 November 2020

Trial information

Trial identification

Sponsor protocol code	D5470C00004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02696902
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC
Sponsor organisation address	One MedImmune Way, Gaithersburg, Maryland, United States, 20878
Public contact	Mark Esser, MedImmune, LLC, +1 301 3986849, information.center@astrazeneca.com
Scientific contact	Mark Esser, MedImmune, LLC, +1 301 3986849, information.center@astrazeneca.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	26 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 December 2019
Global end of trial reached?	Yes
Global end of trial date	04 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of MEDI3902 in reducing the incidence of nosocomial pneumonia caused by Pseudomonas aeruginosa and to evaluate the safety of a single intravenous (IV) dose of MEDI3902 in mechanically-ventilated participants.

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization guideline: Good Clinical Practice, and applicable regulatory requirements. Participants signed an informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 April 2016
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	Austria: 2
Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	France: 74
Country: Number of subjects enrolled	Greece: 19
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	188
EEA total number of subjects	168

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)	89
From 65 to 84 years	97
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 13Apr2016 and 04Dec2019.

Pre-assignment

Screening details:

A total of 188 participants were assigned to the study treatment groups. Out of 188 participants, 4 participants did not receive the study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received single intravenous (IV) dose of placebo matched to MEDI3902.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single intravenous (IV) dose of placebo matched to MEDI3902.

Arm title	MEDI3902 500 mg

Arm description:

Participants received single IV dose of 500 mg MEDI3902.

Arm type	Experimental
Investigational medicinal product name	MEDI3902
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single IV dose of 500 mg of MEDI3902.

Arm title	MEDI3902 1500 mg

Arm description:

Participants received single IV dose of 1500 mg MEDI3902.

Arm type	Experimental
Investigational medicinal product name	MEDI3902
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
Single IV dose of 1500 mg of MEDI3902.

Number of subjects in period 1	Placebo	MEDI3902 500 mg	MEDI3902 1500 mg
Started	85	16	87
Treated	83	16	85
Completed	63	12	59
Not completed	22	4	28
Adverse event, serious fatal	19	3	24
Sponsor's decision	1	-	-
Consent withdrawn by subject	-	-	1
Participant not fit post-randomization	-	-	1
Principal investigator's decision	1	-	-
Transferred to other hospital	1	-	-
Participant not eligible (negative PCR)	-	-	1
Lost to follow-up	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received single intravenous (IV) dose of placebo matched to MEDI3902.	
Reporting group title	MEDI3902 500 mg
Reporting group description:	
Participants received single IV dose of 500 mg MEDI3902.	
Reporting group title	MEDI3902 1500 mg
Reporting group description:	
Participants received single IV dose of 1500 mg MEDI3902.	

Reporting group values	Placebo	MEDI3902 500 mg	MEDI3902 1500 mg
Number of subjects	85	16	87
Age categorical Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	39	7	43
From 65-84 years	44	9	44
85 years and over	2	0	0
Age Continuous Units: Years			
arithmetic mean	64.4	62.7	60.6
standard deviation	± 13.0	± 9.3	± 15.1
Sex: Female, Male Units: Participants			
Female	22	6	32
Male	63	10	55
Race/Ethnicity, Customized Units: Subjects			
Asian	1	0	0
Black or African American	4	0	2
Native Hawaiian or Other Pacific Islander	1	0	0
White	77	16	83
Other	2	0	2

Reporting group values	Total		
Number of subjects	188		

Age categorical Units: Participants			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	89		
From 65-84 years	97		
85 years and over	2		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	60		
Male	128		
Race/Ethnicity, Customized Units: Subjects			
Asian	1		
Black or African American	6		
Native Hawaiian or Other Pacific Islander	1		
White	176		
Other	4		

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received single intravenous (IV) dose of placebo matched to MEDI3902.	
Reporting group title	MEDI3902 500 mg
Reporting group description:	
Participants received single IV dose of 500 mg MEDI3902.	
Reporting group title	MEDI3902 1500 mg
Reporting group description:	
Participants received single IV dose of 1500 mg MEDI3902.	

Primary: Percentage of Participants With Nosocomial Pneumonia Caused by Pseudomonas aeruginosa	
End point title	Percentage of Participants With Nosocomial Pneumonia Caused by Pseudomonas aeruginosa
End point description:	
Percentage of participants with nosocomial pneumonia caused by Pseudomonas aeruginosa is reported. The modified intent to treat (mITT) population was analysed which included all randomized and treated participants, grouped according to assigned treatment.	
End point type	Primary
End point timeframe:	
Day 1 through Day 22	

End point values	Placebo	MEDI3902 500 mg	MEDI3902 1500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	16	85	
Units: Percentage of participants				
number (not applicable)	18.1	12.5	22.4	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	MEDI3902 1500 mg v Placebo
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.491
Method	Poisson regression with robust variance
Parameter estimate	Relative risk reduction
Point estimate	-23.7

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-83.8
upper limit	16.8

Primary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. The TEAEs are defined as events present at baseline that worsened in intensity after administration of study drug or events absent at baseline that emerged after administration of study drug. The As-treated population was analysed which included all treated participants, grouped according to actual treatment received.

End point type	Primary

End point timeframe:

Day 1 through Day 50

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Placebo	MEDI3902 500 mg	MEDI3902 1500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	16	85	
Units: Participants	81	15	84	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment-emergent Serious Adverse Events (TESAEs)[2]

End point description:

An SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. The As-treated population was analysed which included all treated participants, grouped according to actual treatment received.

End point type	Primary

End point timeframe:

Day 1 through Day 50

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Placebo	MEDI3902 500 mg	MEDI3902 1500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	16	85	
Units: Participants	35	4	38	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Treatment-emergent Adverse Events of Special Interest (TEAESI)

End point title	Number of Participants With Treatment-emergent Adverse Events of Special Interest (TEAESI)[3]

End point description:

An AESI is one of scientific and medical interest specific event for understanding of the study drug and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The As-treated population was analysed which included all treated participants, grouped according to actual treatment received.

End point type	Primary

End point timeframe:

Day 1 through Day 50

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Placebo	MEDI3902 500 mg	MEDI3902 1500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	16	85	
Units: Participants	1	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of MEDI3902

End point title	Maximum Observed Concentration (Cmax) of MEDI3902[4]

End point description:

The Cmax of MEDI3902 is reported. The As-treated population was analysed which included all treated participants, grouped according to actual treatment received. Number of Subjects Analyzed denotes the number of participants evaluated for this end point.

End point type	Secondary

End point timeframe:

Day 1 (predose; 0 and 8 hours post dose), Day 2, Day 4, Day 8, Day 15, Day 22, Day 29, and Day 50

Notes:

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

End point values	MEDI3902 500 mg	MEDI3902 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	84		
Units: mcg/mL				
arithmetic mean (standard deviation)	87.6 (± 23.9)	299 (± 94.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From Time Zero to Infinity (AUC0-inf) of MEDI3902

End point title	Area Under the Concentration-time Curve From Time Zero to Infinity (AUC0-inf) of MEDI3902[5]

End point description:

The AUC0-inf of MEDI3902 is reported. The As-treated population was analysed which included all treated participants, grouped according to actual treatment received. Number of Subjects Analyzed denotes the number of participants evaluated for this end point.

End point type	Secondary

End point timeframe:

Day 1 (predose; 0 and 8 hours post dose), Day 2, Day 4, Day 8, Day 15, Day 22, Day 29, and Day 50

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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI3902 500 mg	MEDI3902 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	81		
Units: day*mcg/mL				
arithmetic mean (standard deviation)	440 (± 135)	1510 (± 675)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) of MEDI3902

End point title	Clearance (CL) of MEDI3902[6]

End point description:

The CL of MEDI3902 from body after intrevanous administration of single dose is reported. The As-treated population was analysed which included all treated participants, grouped according to actual treatment received. Number of Subjects Analyzed denotes the number of participants evaluated for this

end point.

End point type	Secondary

End point timeframe:

Day 1 (predose; 0 and 8 hours post dose), Day 2, Day 4, Day 8, Day 15, Day 22, Day 29, and Day 50

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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI3902 500 mg	MEDI3902 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	81		
Units: L/day				
arithmetic mean (standard deviation)	1.31 (± 0.638)	1.27 (± 0.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Maintaining MEDI3902 Serum Levels Above the Target Level (1.7 µg/mL) Through 21 Days Post Dose

End point title	Percentage of Participants Maintaining MEDI3902 Serum Levels Above the Target Level (1.7 µg/mL) Through 21 Days Post Dose[7]

End point description:

Percentage of participants maintaining MEDI3902 serum levels above the target level (1.7 µg/mL) through 21 days post dose is reported. The As-treated population was analysed which included all treated participants, grouped according to actual treatment received. Number of Subjects Analyzed denotes the number of participants evaluated for this end point.

End point type	Secondary

End point timeframe:

Day 1 (predose; 0 and 8 hours post dose), Day 2, Day 4, Day 8, Day 15, and Day 22

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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI3902 500 mg	MEDI3902 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	84		
Units: Percentage of participants				
number (not applicable)	50	80.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half-life (t1/2) of MEDI3902

End point title	Terminal Elimination Half-life (t1/2) of MEDI3902[8]

End point description:

The t1/2 of MEDI3902 is reported. The As-treated population was analysed which included all treated participants, grouped according to actual treatment received. Number of Subjects Analyzed denotes the number of participants evaluated for this end point.

End point type	Secondary

End point timeframe:

Day 1 (predose; 0 and 8 hours post dose), Day 2, Day 4, Day 8, Day 15, Day 22, Day 29, and Day 50

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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI3902 500 mg	MEDI3902 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	81		
Units: day				
arithmetic mean (standard deviation)	6.56 (± 4.03)	5.65 (± 2.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive Anti-drug Antibodies (ADA) to MEDI3902 treatment

End point title	Number of Participants With Positive Anti-drug Antibodies (ADA) to MEDI3902 treatment

End point description:

Number of participants with positive ADA to MEDI3902 treatment is reported. Persistent positive is defined as positive at >= 2 post-baseline assessments (with >= 16 weeks between first and last positive) or positive at last post-baseline assessment. Transient positive is defined as negative at last post-baseline assessment and positive at only one post-baseline assessment or at >= 2 post-baseline assessments (with < 16 weeks between first and last positive). The As-treated population was analysed which included all treated participants, grouped according to actual treatment received.

End point type	Secondary

End point timeframe:

Day 1 (predose), Day 15, Day 29, Day 50

End point values	Placebo	MEDI3902 500 mg	MEDI3902 1500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	16	85	
Units: Participants				
Positive at baseline and post-baseline	3	2	1	
Persistent positive	4	2	4	
Transient positive	2	2	8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 through Day 50	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	MEDI3902 1500 mg
Reporting group description: -	
Reporting group title	MEDI3902 500 mg
Reporting group description: -	

Serious adverse events	Placebo	MEDI3902 1500 mg	MEDI3902 500 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 83 (42.17%)	38 / 85 (44.71%)	4 / 16 (25.00%)
number of deaths (all causes)	19	24	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Vascular disorders			
Shock			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Death			

subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
General physical health deterioration			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	3 / 83 (3.61%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Pyrexia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 83 (1.20%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Asphyxia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Aspiration			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Atelectasis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Lower respiratory tract congestion			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Mediastinal haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Respiratory arrest			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (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
Respiratory failure			
subjects affected / exposed	0 / 83 (0.00%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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

Weaning failure			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (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
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (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
Cardiac arrest			
subjects affected / exposed	5 / 83 (6.02%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 1
Cardiac failure			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Myocarditis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Pulseless electrical activity			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Sinus node dysfunction			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Nervous system disorders			

Brain injury			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Cerebral infarction			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Coma			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Ischaemic stroke			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Seizure			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (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
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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 disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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

Intestinal haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Pancreatitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 83 (3.61%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Polyuria			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acinetobacter bacteraemia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Bacterial sepsis			

subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Biliary tract infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Brain abscess			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Bronchitis bacterial			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Burkholderia cepacia complex infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Candida sepsis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Endocarditis enterococcal			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Klebsiella bacteraemia			

subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (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
Klebsiella sepsis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Peritonitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Pneumonia pseudomonal			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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
Pseudomonal sepsis			
subjects affected / exposed	4 / 83 (4.82%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 4	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	3 / 83 (3.61%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (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

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

Non-serious adverse events	Placebo	MEDI3902 1500 mg	MEDI3902 500 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 83 (95.18%)	82 / 85 (96.47%)	15 / 16 (93.75%)
Vascular disorders			
Artery dissection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Deep vein thrombosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Extremity necrosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Haemodynamic instability			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	7 / 83 (8.43%)	3 / 85 (3.53%)	3 / 16 (18.75%)
occurrences (all)	9	6	5
Hypoperfusion			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	16 / 83 (19.28%)	23 / 85 (27.06%)	1 / 16 (6.25%)
occurrences (all)	21	29	1
Jugular vein thrombosis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Orthostatic hypotension			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Peripheral coldness			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Phlebitis			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Thrombosis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vein disorder			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Vena cava thrombosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Venous thrombosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 83 (2.41%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Catheter site inflammation			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Catheter site pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Complication associated with device			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Generalised oedema			

subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Granuloma			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hyperthermia			
subjects affected / exposed	2 / 83 (2.41%)	2 / 85 (2.35%)	1 / 16 (6.25%)
occurrences (all)	4	2	1
Hypothermia			
subjects affected / exposed	2 / 83 (2.41%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	3	3	0
Localised oedema			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Medical device pain			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Medical device site dermatitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Medical device site haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Mucosal ulceration			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	4 / 83 (4.82%)	3 / 85 (3.53%)	1 / 16 (6.25%)
occurrences (all)	4	4	1
Pain			
subjects affected / exposed	8 / 83 (9.64%)	7 / 85 (8.24%)	0 / 16 (0.00%)
occurrences (all)	15	7	0
Peripheral swelling			

subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	13 / 83 (15.66%)	16 / 85 (18.82%)	1 / 16 (6.25%)
occurrences (all)	20	20	1
Swelling			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Thirst			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Cervical cyst			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Genital pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Oedema genital			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Penile discharge			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Penile oedema			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Prostatitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pruritus genital			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vulval disorder			

subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Acute respiratory failure			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Apnoea			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Aspiration			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Atelectasis			
subjects affected / exposed	4 / 83 (4.82%)	4 / 85 (4.71%)	1 / 16 (6.25%)
occurrences (all)	5	4	1
Bronchial haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Bronchial obstruction			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Bronchial secretion retention			
subjects affected / exposed	2 / 83 (2.41%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Bronchiectasis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Bronchospasm			
subjects affected / exposed	2 / 83 (2.41%)	2 / 85 (2.35%)	1 / 16 (6.25%)
occurrences (all)	2	2	1
Chronic respiratory failure			

subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Chylothorax			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	2 / 83 (2.41%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	2	2	0
Dyspnoea			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Haemoptysis			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Haemothorax			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hiccups			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hypercapnia			
subjects affected / exposed	2 / 83 (2.41%)	5 / 85 (5.88%)	0 / 16 (0.00%)
occurrences (all)	2	8	0
Hyperventilation			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Hypopnoea			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hypoventilation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	2	2	0
Increased bronchial secretion			

subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Increased viscosity of bronchial secretion			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Interstitial lung disease			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Laryngeal oedema			
subjects affected / exposed	3 / 83 (3.61%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	3	2	0
Lung infiltration			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	2 / 16 (12.50%)
occurrences (all)	0	1	2
Pleural disorder			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	2 / 83 (2.41%)	3 / 85 (3.53%)	3 / 16 (18.75%)
occurrences (all)	2	4	3
Pneumonitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pneumothorax			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pulmonary congestion			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Pulmonary embolism			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Pulmonary fistula			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pulmonary oedema			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	5	0
Respiratory acidosis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Respiratory distress			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Respiratory fatigue			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rhonchi			
subjects affected / exposed	2 / 83 (2.41%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Sputum retention			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Tachypnoea			
subjects affected / exposed	2 / 83 (2.41%)	3 / 85 (3.53%)	1 / 16 (6.25%)
occurrences (all)	3	3	1

Throat irritation			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Agitation			
subjects affected / exposed	3 / 83 (3.61%)	3 / 85 (3.53%)	1 / 16 (6.25%)
occurrences (all)	3	3	1
Anxiety			
subjects affected / exposed	4 / 83 (4.82%)	2 / 85 (2.35%)	3 / 16 (18.75%)
occurrences (all)	5	2	3
Apathy			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Compulsive lip biting			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Delirium			
subjects affected / exposed	1 / 83 (1.20%)	5 / 85 (5.88%)	0 / 16 (0.00%)
occurrences (all)	1	5	0
Depression			
subjects affected / exposed	2 / 83 (2.41%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	2	3	0
Depressive symptom			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Disinhibition			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Disorientation			

subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Initial insomnia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	9 / 83 (10.84%)	7 / 85 (8.24%)	0 / 16 (0.00%)
occurrences (all)	10	7	0
Intensive care unit delirium			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nervousness			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Restlessness			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Product issues			
Stent malfunction			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Thrombosis in device			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 83 (4.82%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 83 (3.61%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Blood albumin decreased			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Blood glucose increased			

subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Blood magnesium decreased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Blood potassium decreased			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Blood sodium decreased			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Blood urea increased			
subjects affected / exposed	0 / 83 (0.00%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
C-reactive protein increased			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Inflammatory marker increased			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Oxygen saturation abnormal			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Oxygen saturation decreased			
subjects affected / exposed	3 / 83 (3.61%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	9	10	0
Transaminases increased			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Urine output decreased			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
White blood cell count increased			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
PCO2 increased			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
PO2 decreased			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	3	5	0
Injury, poisoning and procedural complications			
Dialysis related complication			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Endotracheal intubation complication			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Eschar			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Flail chest			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Gastrostomy tube site complication			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Haemodilution			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Inflammation of wound			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Infusion related reaction			

subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Joint dislocation			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Overdose			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Palate injury			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Post procedural haematuria			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Post procedural inflammation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Postoperative hypotension			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Postoperative wound complication			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Procedural haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Procedural hypotension			
subjects affected / exposed	3 / 83 (3.61%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Procedural pain			
subjects affected / exposed	0 / 83 (0.00%)	3 / 85 (3.53%)	1 / 16 (6.25%)
occurrences (all)	0	3	1
Scar			
subjects affected / exposed	2 / 83 (2.41%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Scratch			

subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Seroma			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Stoma site erythema			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tracheal haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Weaning failure			
subjects affected / exposed	2 / 83 (2.41%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	2	2	0
Wound necrosis			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Wound secretion			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 83 (3.61%)	4 / 85 (4.71%)	2 / 16 (12.50%)
occurrences (all)	3	7	2
Atrial tachycardia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Bradycardia			
subjects affected / exposed	2 / 83 (2.41%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	2	5	0

Cardiac arrest			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Cardiac failure			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Cardiac failure congestive			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Cardiogenic shock			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Coronary artery occlusion			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cyanosis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Mitral valve stenosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Supraventricular tachycardia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Tachycardia			
subjects affected / exposed	7 / 83 (8.43%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	11	3	0
Ventricular dysfunction			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Ventricular tachycardia			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Complex regional pain syndrome			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Epilepsy			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Extrapyramidal disorder			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Frontotemporal dementia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	2 / 83 (2.41%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences (all)	3	7	0
Hydrocephalus			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Loss of consciousness			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Metabolic encephalopathy			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Motor dysfunction			

subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Myoclonus			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Paresis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Parkinsonism			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Peripheral motor neuropathy			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Peroneal nerve palsy			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Post cardiac arrest syndrome			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Psychomotor hyperactivity			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	2 / 83 (2.41%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	2	2	0
Syncope			

subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Anaemia of chronic disease			
subjects affected / exposed	4 / 83 (4.82%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences (all)	5	4	0
Blood loss anaemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Haemolytic anaemia			
subjects affected / exposed	5 / 83 (6.02%)	8 / 85 (9.41%)	0 / 16 (0.00%)
occurrences (all)	9	13	0
Iron deficiency anaemia			
subjects affected / exposed	7 / 83 (8.43%)	2 / 85 (2.35%)	1 / 16 (6.25%)
occurrences (all)	10	2	1
Leukocytosis			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Microcytic anaemia			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Normocytic anaemia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Splenomegaly			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	1 / 83 (1.20%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences (all)	2	4	0

Thrombocytosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Excessive cerumen production			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Noninfective conjunctivitis			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Ocular hyperaemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pupils unequal			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	6 / 83 (7.23%)	3 / 85 (3.53%)	2 / 16 (12.50%)
occurrences (all)	6	6	3
Abdominal pain upper			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Aerophagia			

subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Anal incontinence			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Colitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	11 / 83 (13.25%)	11 / 85 (12.94%)	4 / 16 (25.00%)
occurrences (all)	13	11	5
Diarrhoea			
subjects affected / exposed	11 / 83 (13.25%)	12 / 85 (14.12%)	4 / 16 (25.00%)
occurrences (all)	16	14	5
Dysphagia			
subjects affected / exposed	2 / 83 (2.41%)	6 / 85 (7.06%)	0 / 16 (0.00%)
occurrences (all)	2	6	0
Faecaloma			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal oedema			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 83 (2.41%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences (all)	2	1	1
Ileus			

subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Ileus paralytic			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Intestinal dilatation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Lip haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Melaena			
subjects affected / exposed	3 / 83 (3.61%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	3	2	0
Nausea			
subjects affected / exposed	3 / 83 (3.61%)	1 / 85 (1.18%)	4 / 16 (25.00%)
occurrences (all)	5	2	5
Oesophagopleural fistula			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Oral mucosa haematoma			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pancreatic failure			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pancreatic necrosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pancreatitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Perianal erythema			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			

subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Salivary hypersecretion			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	1 / 16 (6.25%)
occurrences (all)	1	2	1
Vomiting			
subjects affected / exposed	3 / 83 (3.61%)	4 / 85 (4.71%)	2 / 16 (12.50%)
occurrences (all)	5	6	4
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Cholelithiasis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Cholestasis			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Drug-induced liver injury			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hepatocellular injury			
subjects affected / exposed	2 / 83 (2.41%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	2	2	0
Ischaemic hepatitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Decubitus ulcer			
subjects affected / exposed	6 / 83 (7.23%)	5 / 85 (5.88%)	0 / 16 (0.00%)
occurrences (all)	6	6	0
Dermatitis			

subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	3 / 83 (3.61%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	5	2	0
Generalised erythema			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 83 (0.00%)	3 / 85 (3.53%)	1 / 16 (6.25%)
occurrences (all)	0	5	1
Rash			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Rash erythematous			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Rash papular			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rash pruritic			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Scab			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Skin irritation			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Skin ulcer haemorrhage			

subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Skin ulcer			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Stasis dermatitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Subcutaneous emphysema			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Swelling face			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 83 (3.61%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Anuria			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Chronic kidney disease			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Haemorrhage urinary tract			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nephrolithiasis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Oliguria			
subjects affected / exposed	5 / 83 (6.02%)	5 / 85 (5.88%)	1 / 16 (6.25%)
occurrences (all)	6	5	1

Polyuria			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Renal cyst			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Renal failure			
subjects affected / exposed	3 / 83 (3.61%)	5 / 85 (5.88%)	0 / 16 (0.00%)
occurrences (all)	3	5	0
Renal impairment			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	1 / 16 (6.25%)
occurrences (all)	1	2	1
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Urinary tract disorder			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Urine abnormality			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Vesical fistula			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Diabetes insipidus			

subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Euthyroid sick syndrome			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hyperprolactinaemia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypothyroidism			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	1 / 16 (6.25%)
occurrences (all)	0	2	1
Bone disorder			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Coccydynia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Exposed bone in jaw			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			

subjects affected / exposed	3 / 83 (3.61%)	2 / 85 (2.35%)	3 / 16 (18.75%)
occurrences (all)	4	2	3
Musculoskeletal stiffness			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Myopathy			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	3 / 83 (3.61%)	3 / 85 (3.53%)	1 / 16 (6.25%)
occurrences (all)	3	3	1
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Acinetobacter infection			
subjects affected / exposed	2 / 83 (2.41%)	5 / 85 (5.88%)	0 / 16 (0.00%)
occurrences (all)	2	5	0
Anal fungal infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Bacteraemia			
subjects affected / exposed	4 / 83 (4.82%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences (all)	4	5	0
Bacterial abdominal infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Bacterial disease carrier			
subjects affected / exposed	1 / 83 (1.20%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	2	5	0
Bacterial infection			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0

Bacterial sepsis			
subjects affected / exposed	0 / 83 (0.00%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences (all)	0	4	0
Bacteriuria			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Bronchitis bacterial			
subjects affected / exposed	2 / 83 (2.41%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	2	2	0
Candida infection			
subjects affected / exposed	2 / 83 (2.41%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	2	2	0
Candiduria			
subjects affected / exposed	2 / 83 (2.41%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Cellulitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Citrobacter bacteraemia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Conjunctivitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Cystitis klebsiella			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Empyema			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Endocarditis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Enterobacter bacteraemia			
subjects affected / exposed	2 / 83 (2.41%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	2	2	0
Enterobacter pneumonia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Enterococcal bacteraemia			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	1 / 16 (6.25%)
occurrences (all)	0	2	1
Enterococcal infection			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Escherichia bacteraemia			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Enterococcal sepsis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Escherichia urinary tract infection			
subjects affected / exposed	5 / 83 (6.02%)	3 / 85 (3.53%)	1 / 16 (6.25%)
occurrences (all)	5	4	2
Eye infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Fungaemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	2 / 83 (2.41%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Genital infection female			
subjects affected / exposed	0 / 83 (0.00%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Haematoma infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Herpes virus infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Infectious pleural effusion			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Klebsiella bacteraemia			
subjects affected / exposed	1 / 83 (1.20%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	1	3	0
Klebsiella infection			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Klebsiella sepsis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Lung infection pseudomonal			
subjects affected / exposed	2 / 83 (2.41%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	5	1	0
Morganella infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	1 / 83 (1.20%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	1	3	0
Oral fungal infection			

subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 83 (1.20%)	3 / 85 (3.53%)	1 / 16 (6.25%)
occurrences (all)	1	3	1
Pneumonia acinetobacter			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Pneumonia bacterial			
subjects affected / exposed	12 / 83 (14.46%)	4 / 85 (4.71%)	2 / 16 (12.50%)
occurrences (all)	13	5	2
Pneumonia escherichia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pneumonia proteus			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pneumonia pseudomonal			
subjects affected / exposed	12 / 83 (14.46%)	13 / 85 (15.29%)	1 / 16 (6.25%)
occurrences (all)	13	15	1
Pneumonia staphylococcal			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Proteus infection			
subjects affected / exposed	4 / 83 (4.82%)	1 / 85 (1.18%)	1 / 16 (6.25%)
occurrences (all)	4	1	2
Pseudomonal bacteraemia			
subjects affected / exposed	6 / 83 (7.23%)	6 / 85 (7.06%)	0 / 16 (0.00%)
occurrences (all)	6	6	0
Pseudomonal sepsis			

subjects affected / exposed	5 / 83 (6.02%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	6	0	0
Pseudomonas bronchitis			
subjects affected / exposed	5 / 83 (6.02%)	4 / 85 (4.71%)	4 / 16 (25.00%)
occurrences (all)	5	4	4
Pseudomonas infection			
subjects affected / exposed	4 / 83 (4.82%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences (all)	4	4	0
Pyuria			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Septic shock			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Serratia bacteraemia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Serratia sepsis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 83 (2.41%)	4 / 85 (4.71%)	1 / 16 (6.25%)
occurrences (all)	2	4	1
Staphylococcal infection			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Staphylococcal sepsis			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Stenotrophomonas infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Stoma site infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Systemic candida			

subjects affected / exposed	3 / 83 (3.61%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Tracheobronchitis			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	1 / 83 (1.20%)	3 / 85 (3.53%)	1 / 16 (6.25%)
occurrences (all)	1	3	2
Urinary tract infection bacterial			
subjects affected / exposed	3 / 83 (3.61%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	3	3	0
Urinary tract infection pseudomonal			
subjects affected / exposed	5 / 83 (6.02%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences (all)	6	4	0
Urinary tract infection staphylococcal			
subjects affected / exposed	2 / 83 (2.41%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Varicella zoster virus infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Alkalosis			
subjects affected / exposed	2 / 83 (2.41%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	2	6	0

Decreased appetite			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Dehydration			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Fluid overload			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Fluid retention			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Hyperammonaemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 83 (1.20%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences (all)	1	5	0
Hyperkalaemia			
subjects affected / exposed	2 / 83 (2.41%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	2	4	0
Hypernatraemia			
subjects affected / exposed	3 / 83 (3.61%)	5 / 85 (5.88%)	1 / 16 (6.25%)
occurrences (all)	3	5	1
Hyperphosphataemia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	4 / 83 (4.82%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	4	3	0

Hypocalcaemia			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Hypoglycaemia			
subjects affected / exposed	0 / 83 (0.00%)	2 / 85 (2.35%)	1 / 16 (6.25%)
occurrences (all)	0	2	1
Hypokalaemia			
subjects affected / exposed	9 / 83 (10.84%)	15 / 85 (17.65%)	1 / 16 (6.25%)
occurrences (all)	12	25	1
Hypomagnesaemia			
subjects affected / exposed	1 / 83 (1.20%)	3 / 85 (3.53%)	0 / 16 (0.00%)
occurrences (all)	1	3	0
Hyponatraemia			
subjects affected / exposed	3 / 83 (3.61%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	3	2	0
Hypophosphataemia			
subjects affected / exposed	0 / 83 (0.00%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences (all)	0	4	0
Hypoproteinaemia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypovolaemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 85 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Metabolic acidosis			
subjects affected / exposed	1 / 83 (1.20%)	2 / 85 (2.35%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Metabolic alkalosis			
subjects affected / exposed	3 / 83 (3.61%)	4 / 85 (4.71%)	0 / 16 (0.00%)
occurrences (all)	3	5	0
Vitamin K deficiency			
subjects affected / exposed	1 / 83 (1.20%)	1 / 85 (1.18%)	0 / 16 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2016	New Onset of Chronic Diseases (NOCDs) as a safety assessment was removed. Blood for culture assessments on Days 2 and 4 were removed from the Schedule of Investigational Product Administration and Follow-up Study Procedures. Clarified that only protein markers of inflammation (only while participant is intubated) in tracheal aspirate will be assessed. Added footnote to clarify that the tracheal aspirate for protein markers of inflammation (only while participant is intubated) sample collected on Day 8 would also be collected on day of extubation if it occurred on day between scheduled assessments. Added tracheal or bronchial (not just tracheal) aspirate may be collected (in intubated participants only) for Gram stain and culture. Clarified that qualitative respiratory culture results would be recorded by all study sites and that quantitative and semi-quantitative respiratory culture results would be recorded by study sites when available. Clarified that chest X-rays performed as part of routine medical care can be used when available. Clarified that respiratory specimen positive for P aeruginosa by culture also includes expectorated sputum. Clarified that a participant is not considered to be mechanically ventilated when an endotracheal or nasotracheal tube is not in place and the participant does not require positive ventilation support for at least 8 hours. Clarified the text to reflect the change in blood collection. Added additional information for the sample size re estimation method. Approximated the antibiotic usage time after randomization from hours to days. Clarified that for participants with P aeruginosa pneumonia, the microbiology culture results would be summarized descriptively for both quantitative and semi-quantitative results, when available. Clarified that no interim analyses were planned during the study.
22 December 2016	Clarified that interactive web response system (IWRS) would be used as a method for assigning participants to treatment groups. Included the rationale for discontinuing enrolment in the 500 mg MEDI3902 group. Modified text to reflect the number of participants who would be enrolled and randomised into the study. Removed the restriction of 75% in either stratum. Updated the study flow diagram. Modified text to reflect the new treatment regimen. Added results from PK study in mice. Modified the text to maintain 1:1 ratio with the placebo group, if the 3000 mg dose was used. Modified text to increase the sequential organ failure assessment (SOFA) score to ≥ 12 (instead of ≥ 9) and added that vasopressors used to improve cerebral perfusion pressure should not be used in the calculation of the cardiovascular component of the SOFA score. Modified text to state that the tracheal/bronchial aspirate (for Gram stain and culture) and expectorated sputum (Gram stain and culture) was to be collected on Day 1 of onset of illness, Day 2, Day 3 and from Day 4 as clinically indicated, instead of daily, until clinical resolution. Modified text that described the reconstitution procedure, dose preparation for MEDI3902 and duration of infusion. Added section describing the unblinding plan and personnel who will remain blinded. Added that if a dose adjustment was made from 1500 mg MEDI3902 to 3000 mg MEDI3902, the key efficacy analyses would be based on 3000 mg MEDI3902 and placebo participants and that the participants who received 500 mg or 1500 mg MEDI3902 would be summarized descriptively. Added section to describe the PK interim analysis. Modified the definition of overdose.

06 June 2018	Removed the secondary objective: To evaluate the effect of MEDI3902 in reducing the incidence of nosocomial pneumonia caused by P aeruginosa by mechanical ventilation status. Removed the secondary endpoints corresponding to the secondary objective above. Removed "white blood cell count and differential" from the list of biomarkers that were to be analysed from tracheal aspirate. Modified text to reflect change in terms of stratification by receipt of anti-P aeruginosa antibiotic treatment (no antibiotics use, duration of =< 72 hours, duration of > 72 hours) within 96 hours prior to randomisation. Modified exclusion criteria to state that only receipt of systemic colistin and aerosolized colistin anti-P aeruginosa antibiotics for > 72 hours within 96 hours prior to randomisation or anticipated ongoing receipt of the aforementioned anti-P aeruginosa antibiotics are exclusionary. Removed "blood markers of inflammation" from routine schedule of events at Day 1, pre dose and Day 8. Added tracheobronchitis as suspected outcome in Schedule of Procedures for Participants With Suspected or Confirmed Pneumonia, Tracheobronchitis or Bacteremia, prompting Day 1 onset visit assessments. Clarified the definition of tracheobronchitis. Clarified that if the duration of the infusion exceeded 8 hours for the 1500 mg MEDI3902/placebo groups and 12 hours (in case of dose adjustment) for the 3000 mg MEDI3902/placebo groups, the medical monitor should be notified immediately. Changed primary efficacy population to mITT rather than ITT. Removed secondary efficacy endpoint analyses. Added clarification to primary efficacy analysis. Added Appendix 10 with list of study-specified anti-P aeruginosa antibiotics for stratification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported