Clinical trial results:
A Phase 2 Randomised, Double-blind, Placebo-controlled, Single-dose, Dose-ranging Study of the Efficacy and Safety of MEDI4893, a Human Monoclonal Antibody Against Staphylococcus aureus Alpha Toxin in Mechanically Ventilated Adult Subjects

Summary

EudraCT number	2014-001097-34
Trial protocol	BE GR DE ES CZ PT HU GB IE
Global end of trial date	02 October 2018

Results information

Result version number	v1
This version publication date	16 October 2019
First version publication date	16 October 2019

Trial information

Trial identification

Sponsor protocol code	CD-ID-MEDI4893-1139

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02296320
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC
Sponsor organisation address	One MedImmune Way, Gaithersburg, United States, 20878
Public contact	Hasan S. Jafri, MedImmune, LLC, MD +1 3013984431, information.center@astrazeneca.com
Scientific contact	Hasan S. Jafri, MedImmune, LLC, MD +1 3013984431, 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	14 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2018
Global end of trial reached?	Yes
Global end of trial date	02 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the safety and efficacy of a single intravenous (IV) dose of MEDI4893 in reducing the incidence of Staphylococcus aureus pneumonia.

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	10 October 2014
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	Belgium: 26
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 119
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	Switzerland: 16
Worldwide total number of subjects	213
EEA total number of subjects	197

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)	139
From 65 to 84 years	70
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 10Oct2014 and 02Oct2018.

Pre-assignment

Screening details:

A total of 767 participants consented to participate in the study, of which 554 were screen failures. A total of 213 participants were randomised in the study. Out of 213 randomised participates, 2 participants were not treated with the study drug and therefore the data for "Baseline Characteristics" were not collected.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received a single intravenous (IV) dose of placebo matched to MEDI4893 on Day 1 of the study.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

A single IV dose matched to MEDI4893 on Day 1 of the study.

Arm title	MEDI4893 2000 mg

Arm description:

Participants received a single IV dose of MEDI4893 2000 milligrams (mg) on Day 1 of the study.

Arm type	Experimental
Investigational medicinal product name	MEDI4893
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

A single IV dose of 2000 mg on Day 1 of the study.

Arm title	MEDI4893 5000 mg

Arm description:

Participants received a single IV dose of MEDI4893 5000 mg on Day 1 of the study.

Arm type	Experimental

Investigational medicinal product name	MEDI4893
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

A single IV dose of 5000 mg on Day 1 of the study.

Number of subjects in period 1[1]	Placebo	MEDI4893 2000 mg	MEDI4893 5000 mg
Started	100	15	96
Completed	67	10	59
Not completed	33	5	37
Adverse event, serious fatal	24	3	27
Consent withdrawn by subject	4	-	2
Not - specified	-	-	1
Lost to follow-up	5	2	7

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Total subjects enrolled worldwide were 213; of which 2 subjects were randomized but not treated. These 2 subjects were not included in As-treated population and data for these subjects were not captured for baseline characteristics.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received a single intravenous (IV) dose of placebo matched to MEDI4893 on Day 1 of the study.	
Reporting group title	MEDI4893 2000 mg
Reporting group description:	
Participants received a single IV dose of MEDI4893 2000 milligrams (mg) on Day 1 of the study.	
Reporting group title	MEDI4893 5000 mg
Reporting group description:	
Participants received a single IV dose of MEDI4893 5000 mg on Day 1 of the study.	

Reporting group values	Placebo	MEDI4893 2000 mg	MEDI4893 5000 mg
Number of subjects	100	15	96
Age categorical Units: Subjects			
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)	67	13	58
From 65-84 years	30	2	37
85 years and over	3	0	1
Age Continuous Units: Years			
arithmetic mean	55.7	52.5	57.7
standard deviation	± 16.6	± 14.6	± 15.7
Sex: Female, Male Units: Subjects			
Female	45	5	37
Male	55	10	59
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	1	2
White	97	13	94
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	0	4

Not Hispanic or Latino	96	15	92
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	211		
Age categorical Units: Subjects			
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)	138		
From 65-84 years	69		
85 years and over	4		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	87		
Male	124		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	6		
White	204		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8		
Not Hispanic or Latino	203		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received a single intravenous (IV) dose of placebo matched to MEDI4893 on Day 1 of the study.	
Reporting group title	MEDI4893 2000 mg
Reporting group description:	
Participants received a single IV dose of MEDI4893 2000 milligrams (mg) on Day 1 of the study.	
Reporting group title	MEDI4893 5000 mg
Reporting group description:	
Participants received a single IV dose of MEDI4893 5000 mg on Day 1 of the study.	

Primary: Percentage of Participants With Endpoint Adjudication Committee-Determined (EAC) Staphylococcus aureus (S aureus) Pneumonia

End point title	Percentage of Participants With Endpoint Adjudication Committee-Determined (EAC) Staphylococcus aureus (S aureus) Pneumonia
End point description:	
Percentage of participants with EAC-Determined S aureus pneumonia is reported. Modified Intent-to-treat (mITT) population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to their randomised treatment group.	
End point type	Primary
End point timeframe:	
Day 1 through Day 31	

End point values	Placebo	MEDI4893 2000 mg	MEDI4893 5000 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	15	96	
Units: Percentage of Participants				
number (not applicable)	26.0	20	17.7	

Statistical analyses

Statistical analysis title	Comparison of EAC-Determined S aureus pneumonia
Statistical analysis description:	
The key efficacy analyses were based on 5000 mg MEDI4893 and placebo. Participants who received 2000 mg MEDI4893 were summarised descriptively.	
Comparison groups	Placebo v MEDI4893 5000 mg

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.166
Method	Poisson regression with robust variance
Parameter estimate	Relative risk reduction
Point estimate	31.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.5
upper limit	56.8

Primary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) Through 31 Days

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) Through 31 Days[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. 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. As-treated population was analysed for this end point, which included all participants, who received any dose of study drug and analysed according to the treatment they actually received.

End point type	Primary

End point timeframe:

Day 1 through Day 31

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	MEDI4893 2000 mg	MEDI4893 5000 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	15	96	
Units: Participants	90	15	87	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With TEAEs Through 91 Days

End point title	Number of Participants With TEAEs Through 91 Days[2]

End point description:

An AE is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. 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. As-treated population was analysed for this end point, which included all participants, who received any dose of study drug and analysed according to the treatment they actually

received.

End point type	Primary

End point timeframe:

Day 1 through Day 91

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	MEDI4893 2000 mg	MEDI4893 5000 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	15	96	
Units: Participants	92	15	89	

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)[3]

End point description:

A serious adverse event (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. 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. As-treated population was analysed for this end point, which included all participants, who received any dose of study drug and analysed according to the treatment they actually received.

End point type	Primary

End point timeframe:

Day 1 through Day 191

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	MEDI4893 2000 mg	MEDI4893 5000 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	15	96	
Units: Participants	40	7	50	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Adverse Events of Special Interest (AESIs)

End point title	Number of Participants With Adverse Events of Special Interest (AESIs)[4]

End point description:

An AESI is one of scientific and medical interest specific to understanding of the study drug and may have required close monitoring and rapid communication by the investigator to the sponsor. An AESI may have been serious or non-serious. As-treated population was analysed for this end point, which included all participants, who received any dose of study drug and analysed according to the treatment they actually received.

End point type	Primary

End point timeframe:

Day 1 through Day 191

Notes:

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

End point values	Placebo	MEDI4893 2000 mg	MEDI4893 5000 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	15	96	
Units: Participants	0	4	3	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With New Onset Chronic Diseases (NOCDs)

End point title	Number of Participants With New Onset Chronic Diseases (NOCDs)[5]

End point description:

An NOCD defined as a newly diagnosed medical condition that is of a chronic, ongoing nature. It is observed after receiving the study drug and is assessed by the investigator as medically significant. As-treated population was analysed for this end point, which included all participants, who received any dose of study drug and analysed according to the treatment they actually received.

End point type	Primary

End point timeframe:

Day 1 through Day 191

Notes:

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

End point values	Placebo	MEDI4893 2000 mg	MEDI4893 5000 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	15	96	
Units: Participants	2	0	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of MEDI4893

End point title	Maximum Observed Serum Concentration (Cmax) of

End point description:

Maximum observed serum concentration (Cmax) of MEDI4893 is reported. An Intent-to-treat (ITT) population was analysed for this endpoint, which included all randomised participants who were analysed according to their randomised treatment group and had quantifiable pharmacokinetic (PK) samples.

End point type	Secondary

End point timeframe:

Day 1 (Pre-dose, end of the infusion, 8 and 24 hours post dose), and on Days 4, 8, 15, 22, 31, 61, and 91

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	MEDI4893 2000 mg	MEDI4893 5000 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	94		
Units: µg/mL				
arithmetic mean (standard deviation)	471.9 (± 123.0)	1143.7 (± 375.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration Time Curve From Time Zero to Last Measurable Concentration (AUC [0-Last]) of MEDI4893

End point title	Area Under the Serum Concentration Time Curve From Time Zero to Last Measurable Concentration (AUC [0-Last]) of MEDI4893[7]

End point description:

Area under the serum concentration time curve from time zero to last measurable concentration ([AUC 0-last]) of MEDI4893 is reported. An ITT population was analysed for this endpoint, which included all randomised participants who were analysed according to their randomised treatment group and had quantifiable PK samples.

End point type	Secondary

End point timeframe:

Day 1 (Pre-dose, end of the infusion, 8 and 24 hours post dose), and on Days 4, 8, 15, 22, 31, 61, and 91

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	MEDI4893 2000 mg	MEDI4893 5000 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	94		
Units: day*µg/mL				
arithmetic mean (standard deviation)	9045.5 (± 5383.1)	20127.5 (± 12852.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Serum Concentration of MEDI4893 at 30 Days Post Dose (C30)

End point title	Observed Serum Concentration of MEDI4893 at 30 Days Post Dose (C30)[8]

End point description:

Observed serum concentration of MEDI4893 at 30 days post dose (C30) is reported. An ITT population was analysed for this endpoint, which included all randomised participants who were analysed according to their randomised treatment group and had quantifiable PK samples.

End point type	Secondary

End point timeframe:

Day 1 (Pre-dose, end of the infusion, 8 and 24 hours post dose), and on Days 4, 8, 15, 22, and 30

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	MEDI4893 2000 mg	MEDI4893 5000 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	68		
Units: µg/mL				
arithmetic mean (standard deviation)	122.0 (± 65.0)	295.9 (± 130.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Serum Concentration of MEDI4893 at 90 Days Post Dose (C90)

End point title	Observed Serum Concentration of MEDI4893 at 90 Days Post Dose (C90)[9]

End point description:

Observed serum concentration of MEDI4893 at 90 days post dose (C90) is reported. An ITT population was analysed for this endpoint, which included all randomised participants who were analysed according to their randomised treatment group and had quantifiable PK samples.

End point type	Secondary

End point timeframe:

Day 1 (Pre-dose, end of the infusion, 8 and 24 hours post dose), and on Days 4, 8, 15, 22, 31, 61, and 90

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

End point values	MEDI4893 2000 mg	MEDI4893 5000 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	54		
Units: µg/mL				
arithmetic mean (standard deviation)	71.5 (± 35.5)	192.0 (± 84.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive Anti-Drug Antibodies (ADA) Titre to MEDI4893

End point title	Number of Participants With Positive Anti-Drug Antibodies (ADA) Titre to MEDI4893

End point description:

Number of participants with positive ADA titre to MEDI4893 are reported. As-treated population was analysed for this end point, which included all participants, who received any dose of study drug and analysed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Days 1 (Pre dose), 31, 61, and, 91

End point values	Placebo	MEDI4893 2000 mg	MEDI4893 5000 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	15	96	
Units: Participants				
Positive at baseline	3	0	2	
Positive post-baseline	5	0	0	
Positive at baseline and post-baseline	2	0	0	
Not detected at baseline; positive post-baseline	3	0	0	
Positive at baseline; not detected post-baseline	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: SAEs: Day 1 through Day 191 AEs: Day 1 through Day 91	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: Participants received a single IV dose of placebo matched to MEDI4893 on Day 1 of the study	
Reporting group title	MEDI4893 2000 mg
Reporting group description: Participants received a single IV dose of MEDI4893 2000 mg on Day 1 of the study.	
Reporting group title	MEDI4893 5000 mg
Reporting group description: Participants received a single IV dose of MEDI4893 5000 mg on Day 1 of the study.	

Serious adverse events	Placebo	MEDI4893 2000 mg	MEDI4893 5000 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 100 (40.00%)	7 / 15 (46.67%)	50 / 96 (52.08%)
number of deaths (all causes)	24	3	27
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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

Hepatocellular carcinoma			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal cancer			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Hypotension			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Brain death			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bronchospasm			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Haemoptysis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Hypoxia			
subjects affected / exposed	3 / 100 (3.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Laryngeal oedema			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pleural effusion			

subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Pulmonary embolism			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	5 / 96 (5.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Stridor			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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			
Coma scale abnormal			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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			
Extradural haematoma			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (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
Tracheostomy malfunction			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weaning failure			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2

Cardiac failure congestive			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (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
Congestive cardiomyopathy			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Nervous system disorders			
Brain hypoxia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Brain oedema			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Brain stem stroke			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coma			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	5 / 96 (5.21%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 4
Depressed level of consciousness			

subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Epilepsy			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Hydrocephalus			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnic coma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Intracranial pressure increased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intraventricular haemorrhage			

subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Ischaemic stroke			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	3 / 96 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Multiple system atrophy			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myasthenia gravis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Partial seizures			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ruptured cerebral aneurysm			

subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Status epilepticus			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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			
Abdominal pain			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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 haemorrhage			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intestinal ischaemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Strangulated umbilical hernia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
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			

Hepatocellular injury			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infections and infestations			
Acinetobacter infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Bacteraemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Bacterial sepsis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain abscess			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Bronchitis			

subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
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	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis enterococcal			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis staphylococcal			

subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (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			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (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	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia serratia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Pneumonia staphylococcal			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Sepsis			

subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Serratia infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serratia sepsis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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
Staphylococcal infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creutzfeldt-jakob disease			

subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (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

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

Non-serious adverse events	Placebo	MEDI4893 2000 mg	MEDI4893 5000 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 100 (90.00%)	15 / 15 (100.00%)	85 / 96 (88.54%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Leiomyoma			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Osteoma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Haemodynamic instability			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	3	1	0
Hot flush			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	8 / 100 (8.00%)	1 / 15 (6.67%)	7 / 96 (7.29%)
occurrences (all)	8	1	7
Hypotension			
subjects affected / exposed	2 / 100 (2.00%)	1 / 15 (6.67%)	7 / 96 (7.29%)
occurrences (all)	3	2	10
Jugular vein thrombosis			

subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Peripheral venous disease			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Phlebitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Shock			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Thrombophlebitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Venous thrombosis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Generalised oedema			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	3	0	1
Hypothermia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Hyperthermia			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	4	0	1
Implant site haematoma			

subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Infusion site extravasation			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Localised oedema			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Medical device site pain			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	3 / 96 (3.13%)
occurrences (all)	3	0	3
Oedema peripheral			
subjects affected / exposed	3 / 100 (3.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	3	1	0
Pyrexia			
subjects affected / exposed	15 / 100 (15.00%)	2 / 15 (13.33%)	8 / 96 (8.33%)
occurrences (all)	26	5	9
Vascular complication associated with device			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Male genital tract fistula			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Prostatitis			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	1	1	0
Vaginal discharge			

subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	2
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Acute respiratory failure			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Asthma			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Atelectasis			
subjects affected / exposed	3 / 100 (3.00%)	1 / 15 (6.67%)	7 / 96 (7.29%)
occurrences (all)	5	1	7
Bronchial disorder			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Bronchial hyperreactivity			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Bronchial obstruction			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Bronchial secretion retention			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Bronchospasm			
subjects affected / exposed	4 / 100 (4.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	4	0	2
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Cough			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Dyspnoea			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Haemoptysis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Hiccups			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Hypercapnia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Hypoxia			
subjects affected / exposed	2 / 100 (2.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	6	1	0
Increased bronchial secretion			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	2	0	1
Increased viscosity of bronchial secretion			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	2	0	1
Laryngeal dyspnoea			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0

Laryngeal granuloma			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Laryngeal oedema			
subjects affected / exposed	6 / 100 (6.00%)	2 / 15 (13.33%)	1 / 96 (1.04%)
occurrences (all)	6	2	1
Laryngeal pain			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Laryngeal ulceration			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Lung disorder			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	4 / 100 (4.00%)	0 / 15 (0.00%)	6 / 96 (6.25%)
occurrences (all)	5	0	6
Pneumomediastinum			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Pneumonia aspiration			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	2	0	1
Pneumothorax			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Pneumothorax spontaneous			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Pulmonary embolism			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	3	0	0

Pulmonary oedema			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Rales			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Respiratory acidosis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Respiratory disorder			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Respiratory tract congestion			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Tachypnoea			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Agitation			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	6 / 96 (6.25%)
occurrences (all)	4	0	6
Anxiety			
subjects affected / exposed	5 / 100 (5.00%)	1 / 15 (6.67%)	8 / 96 (8.33%)
occurrences (all)	5	1	8
Confusional state			
subjects affected / exposed	2 / 100 (2.00%)	1 / 15 (6.67%)	5 / 96 (5.21%)
occurrences (all)	2	1	7
Delirium			

subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	2 / 100 (2.00%)	1 / 15 (6.67%)	4 / 96 (4.17%)
occurrences (all)	2	1	4
Flat affect			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Hallucination, visual			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Initial insomnia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	4 / 100 (4.00%)	1 / 15 (6.67%)	5 / 96 (5.21%)
occurrences (all)	4	1	5
Organic brain syndrome			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Stress			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences (all)	0	1	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Blood potassium decreased			

subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Body temperature increased			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	3	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
International normalised ratio increased			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Liver function test abnormal			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Mononucleosis heterophile test positive			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Pancreatic enzymes increased			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Transaminases increased			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Endotracheal intubation complication			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Eschar			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Facial bones fracture			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	2	0	2
Infusion related reaction			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences (all)	0	1	2
Mechanical ventilation complication			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Post procedural haematoma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Postoperative wound complication			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Procedural haemorrhage			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Procedural hypotension			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	1	0	2
Spinal compression fracture			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0

Tracheostomy malfunction			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Traumatic shock			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Unintentional medical device removal			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Vasoplegia syndrome			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Weaning failure			
subjects affected / exposed	2 / 100 (2.00%)	1 / 15 (6.67%)	3 / 96 (3.13%)
occurrences (all)	2	1	3
Congenital, familial and genetic disorders			
Muscular dystrophy			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Right-to-left cardiac shunt			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Arrhythmia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Arrhythmia supraventricular			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Atrial fibrillation			
subjects affected / exposed	3 / 100 (3.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences (all)	3	1	2
Atrial flutter			

subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Atrial thrombosis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Atrioventricular block complete			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Atrioventricular block second degree			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Bradycardia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	1	0	2
Cardiac arrest			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Cardiac failure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Left ventricular dysfunction			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Mitral valve incompetence			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Pericardial effusion			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Supraventricular tachycardia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	1	1	0
Tachycardia			

subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	3 / 96 (3.13%)
occurrences (all)	3	0	3
Ventricular extrasystoles			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Ventricular tachycardia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Aphasia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Aphonia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Cerebral ischaemia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Cerebrovascular accident			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Cognitive disorder			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Diabetic hyperosmolar coma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Disturbance in attention			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Dysaesthesia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1

Dysarthria			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Encephalitis autoimmune			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Epilepsy			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	3 / 100 (3.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences (all)	3	1	3
Hemiplegia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Hypoglossal nerve paralysis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Intracranial pressure increased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences (all)	0	1	2
Multiple system atrophy			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Muscle tone disorder			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Myasthenia gravis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Myelopathy			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0

Myoclonic epilepsy			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Neuralgia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	1	0	2
Neurological decompensation			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Paraplegia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Quadriplegia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Sciatica			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Seizure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	1	0	2
Subdural hygroma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Vasculitis cerebral			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Vocal cord paresis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 100 (12.00%)	2 / 15 (13.33%)	11 / 96 (11.46%)
occurrences (all)	24	2	11
Coagulopathy			

subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	1	0	2
Iron deficiency anaemia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	1	1	0
Normochromic anaemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Thrombocytosis			
subjects affected / exposed	3 / 100 (3.00%)	1 / 15 (6.67%)	6 / 96 (6.25%)
occurrences (all)	3	1	6
Ear and labyrinth disorders			
Excessive cerumen production			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Eyelid ptosis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Keratitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	4 / 100 (4.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	5	1	1
Abdominal pain upper			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Barrett's oesophagus			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	15 / 100 (15.00%)	1 / 15 (6.67%)	7 / 96 (7.29%)
occurrences (all)	16	1	7
Diarrhoea			
subjects affected / exposed	8 / 100 (8.00%)	3 / 15 (20.00%)	8 / 96 (8.33%)
occurrences (all)	11	4	13
Dysphagia			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	4 / 96 (4.17%)
occurrences (all)	3	0	4
Faecaloma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Gastrointestinal haemorrhage			
subjects affected / exposed	5 / 100 (5.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	5	0	1
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal obstruction			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Haematemesis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	2
Ileus paralytic			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Impaired gastric emptying			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	4 / 96 (4.17%)
occurrences (all)	3	0	5
Oesophagitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Pancreatic disorder			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Salivary hypersecretion			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	6 / 100 (6.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	6	0	0
Hepatobiliary disorders			
Biliary cirrhosis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Cholestasis			

subjects affected / exposed	4 / 100 (4.00%)	4 / 15 (26.67%)	7 / 96 (7.29%)
occurrences (all)	4	4	7
Hepatic function abnormal			
subjects affected / exposed	0 / 100 (0.00%)	2 / 15 (13.33%)	0 / 96 (0.00%)
occurrences (all)	0	3	0
Hepatocellular injury			
subjects affected / exposed	5 / 100 (5.00%)	4 / 15 (26.67%)	6 / 96 (6.25%)
occurrences (all)	5	4	6
Hyperbilirubinaemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Hypertransaminasaemia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Jaundice cholestatic			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Liver disorder			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Blister			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Decubitus ulcer			
subjects affected / exposed	4 / 100 (4.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	5	1	1
Dermatitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Dermatitis diaper			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1

Dry skin			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Generalised erythema			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Pruritus generalised			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Purpura			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	3	0	1
Rash maculo-papular			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Rosacea			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	1	0	2

Skin lesion			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Skin ulcer			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences (all)	1	1	2
Bladder spasm			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Chronic kidney disease			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	0 / 100 (0.00%)	2 / 15 (13.33%)	2 / 96 (2.08%)
occurrences (all)	0	2	2
Hypertonic bladder			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Oliguria			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	3 / 96 (3.13%)
occurrences (all)	1	0	3
Polyuria			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Renal failure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Renal impairment			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Urinary retention			

subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Goitre			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Hyperthyroidism			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Hypothyroidism			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Amyotrophy			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Back pain			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Bone pain			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Joint stiffness			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Muscle haemorrhage			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Muscular weakness			

subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	3 / 96 (3.13%)
occurrences (all)	1	0	3
Musculoskeletal pain			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Myalgia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Myopathy			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	1	0	2
Neck pain			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	3	0	3
Torticollis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Abscess bacterial			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Acinetobacter bacteraemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Bacteraemia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	2	0	2
Bacterial disease carrier			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Bacterial pyelonephritis			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	1	1	0

Bacterial sepsis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Bacteroides bacteraemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Bronchitis bacterial			
subjects affected / exposed	5 / 100 (5.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	6	0	2
Bronchitis pneumococcal			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Citrobacter infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Citrobacter sepsis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	4	0	2
Cystitis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Cytomegalovirus infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Device related infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Enterobacter bacteraemia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1

Enterobacter infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	2	0
Enterobacter pneumonia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Enterococcal bacteraemia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Enterococcal infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Enterococcal sepsis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Epididymitis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Escherichia bacteraemia			
subjects affected / exposed	2 / 100 (2.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	2	1	0
Escherichia infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Escherichia sepsis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Escherichia urinary tract infection			
subjects affected / exposed	14 / 100 (14.00%)	4 / 15 (26.67%)	18 / 96 (18.75%)
occurrences (all)	18	4	23
Fungal infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Fungal skin infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1

Genital herpes			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Haemophilus infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Helicobacter gastritis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	1	1	0
Infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Infectious pleural effusion			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Klebsiella bacteraemia			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	3	0	0
Klebsiella infection			
subjects affected / exposed	2 / 100 (2.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences (all)	2	1	2
Laryngitis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Localised infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Meningitis bacterial			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Moraxella infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1

Morganella infection			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	5	0	2
Nasopharyngitis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	2	0	1
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Otitis externa			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	1	0	2
Pneumonia bacterial			
subjects affected / exposed	17 / 100 (17.00%)	1 / 15 (6.67%)	7 / 96 (7.29%)
occurrences (all)	17	1	7
Pneumonia escherichia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	2
Pneumonia haemophilus			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Pneumonia klebsiella			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Pneumonia moraxella			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0

Pneumonia pseudomonal			
subjects affected / exposed	4 / 100 (4.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	4	0	0
Pneumonia serratia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Pneumonia staphylococcal			
subjects affected / exposed	13 / 100 (13.00%)	2 / 15 (13.33%)	13 / 96 (13.54%)
occurrences (all)	13	2	13
Postoperative wound infection			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Proteus infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences (all)	0	1	2
Pseudomembranous colitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	1	1	0
Pseudomonas bronchitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Pseudomonas infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Puncture site abscess			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Serratia bacteraemia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Serratia infection			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	2	0	1

Sinusitis			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	3	0	2
Staphylococcal bacteraemia			
subjects affected / exposed	6 / 100 (6.00%)	1 / 15 (6.67%)	3 / 96 (3.13%)
occurrences (all)	7	1	3
Staphylococcal infection			
subjects affected / exposed	4 / 100 (4.00%)	0 / 15 (0.00%)	4 / 96 (4.17%)
occurrences (all)	5	0	4
Staphylococcal sepsis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Staphylococcal skin infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Streptococcal bacteraemia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences (all)	1	1	2
Streptococcal infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Systemic infection			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Tracheobronchitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	2	0	4
Urinary tract infection bacterial			
subjects affected / exposed	2 / 100 (2.00%)	1 / 15 (6.67%)	3 / 96 (3.13%)
occurrences (all)	2	1	3
Urinary tract infection fungal			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1

Urinary tract infection pseudomonal			
subjects affected / exposed	3 / 100 (3.00%)	1 / 15 (6.67%)	4 / 96 (4.17%)
occurrences (all)	3	1	4
Urinary tract infection staphylococcal			
subjects affected / exposed	2 / 100 (2.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	2	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Wound infection bacterial			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	3 / 96 (3.13%)
occurrences (all)	2	0	3
Wound infection staphylococcal			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Cerebral salt-wasting syndrome			
subjects affected / exposed	1 / 100 (1.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	1	1	0
Fluid overload			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	2	1
Folate deficiency			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Gout			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	2	0	2
Hyperglycaemia			
subjects affected / exposed	4 / 100 (4.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	4	1	1
Hyperkalaemia			

subjects affected / exposed	2 / 100 (2.00%)	1 / 15 (6.67%)	2 / 96 (2.08%)
occurrences (all)	2	2	2
Hyperlactacidaemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Hypernatraemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	1	0	2
Hypoalbuminaemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	3	0	2
Hypoglycaemia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	3	0	0
Hypokalaemia			
subjects affected / exposed	7 / 100 (7.00%)	1 / 15 (6.67%)	11 / 96 (11.46%)
occurrences (all)	9	2	13
Hypomagnesaemia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	2 / 96 (2.08%)
occurrences (all)	0	0	2
Hyponatraemia			
subjects affected / exposed	4 / 100 (4.00%)	1 / 15 (6.67%)	4 / 96 (4.17%)
occurrences (all)	5	1	5
Hypophosphataemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	4 / 96 (4.17%)
occurrences (all)	1	0	4
Hypoproteinaemia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	2	0	1
Hypovolaemia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	0 / 96 (0.00%)
occurrences (all)	0	3	0
Iron deficiency			

subjects affected / exposed	0 / 100 (0.00%)	1 / 15 (6.67%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Metabolic alkalosis			
subjects affected / exposed	3 / 100 (3.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	3	0	0
Vitamin b12 deficiency			
subjects affected / exposed	1 / 100 (1.00%)	0 / 15 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Vitamin k deficiency			
subjects affected / exposed	0 / 100 (0.00%)	0 / 15 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2014	Text was added to indicate that enrolment would continue in only the 5000 mg MEDI4893 and placebo arms during interim analyses. A second interim analysis for futility assessment was added to be conducted when approximately 33% to 40% of the enrolled participants were followed through 30 days post dose. Under Microbiologic confirmation, it was clarified that at least one of the bulleted confirmations (ie, not just the first bullet) should be obtained within 24 hours of onset of the event for mechanically ventilated participants and within 72 hours of onset of the event for non-mechanically ventilated participants. Added a section for unblinding for futility analysis purposes. The point at which the sample size may be modified was changed from after 40% to 50% of participants enrolled to after 33% to 40% of participants enrolled, and the sample size reassessment was to be performed prior to the futility assessment. Added the interim analysis for futility.
04 June 2015	Modified text to indicate that the data monitoring committee (DMC) would review pharmacokinetics (PK) data and recommend dose adjustment or study termination during the interim analysis. Modified exclusion criterion for Sequential Organ Failure Assessment (SOFA) score based on the Glasgow Coma Scale score. Modified text to clarify that the criterion of dullness to percussion was not elicited by auscultation and it was a separate criterion. It was clarified that the acute changes in PaO2/FiO2 have to be maintained for at least 4 hours. Added details regarding the PK analysis and presentation to the DMC to further describe how the DMC would recommend dose adjustments or potential study termination. Modified text to note that assessment of time to first S aureus pneumonia might have been analysed by survival methods, which could have been potentially broader than the specific Kaplan-Meier approach originally indicated. In addition, language for subgroup analysis was modified to match the Statistical Analysis Plan. It was added that the DMC would be responsible for recommending dose adjustment or potential study termination.
14 August 2015	Tracheal/bronchial aspirates for both Gram stain and culture were added to the screening procedures and removed from the post-dose procedures. Clarified that the adjudication committee could have requested to review all data relevant to a potential case, including radiographic and imaging studies, as well as other clinical and/or microbiologic data.

20 October 2016	Recommended 2000 mg MEDI4893 group to be discontinued and no dose adjustment to be made to 3000 mg. New participants will be enrolled and randomised to 1 of 2 treatment groups: 5000 mg MEDI4893 or placebo. Change in stratification by receipt of anti-S aureus systemic antibiotic within 72 hours prior to randomisation. Restriction that no more than ~75% of study population would consist of participants in either stratification level of prior anti-S aureus systemic antibiotic was removed. Modified inclusion criteria as: new follow-up duration of 190 days post dose instead of 360 days. Modified exclusion criteria as: to exclude enrolment of participants who received anti-S aureus antibiotics antibiotics for > 48 hours within 72 hours prior to randomisation; exclude enrolment of participants with SOFA score of >= 9 at time of randomisation and to clarify that vasopressors used only to improve cerebral perfusion pressure will not entered in the calculation of cardiovascular component of SOFA score; allow enrolment of participants with asymptomatic human immunodeficiency virus infection; and change time frame for exclusion of patients receiving chemotherapy from 6 months to 2 months. Specimen of expectorated sputum is acceptable for microbiologic confirmation in non- intubated participants but met protocol definition of mechanical ventilation. Participant was not considered mechanically ventilated when endotracheal/nasotracheal tube was not in place and did not require positive ventilation support for at least 8 hours. No adjustments were made for 2000 mg dose when discontinued; 3000 mg dose was removed from key efficacy analyses. Sample size methodology was modified to use Poisson regression with robust variance
15 March 2018	Objective "To evaluate the effect of MEDI4893 in reducing the incidence of S aureus pneumonia by mechanical ventilation status" and corresponding endpoint was removed. Revised timelines for analysis of exploratory endpoints 1 to 8, 12, and 15 to 30 days post dose only; 90 days post dose removed. Number of participants to be enrolled reduced from 285 to ~221. Modified power calculation from 80% to 70%; removed text describing sample size reassessment and futility analysis. Stage 1 analysis to be conducted after last participant completed follow-up through 30 days post dose (instead of 90 days). Safety, serum PK and antidrug antibody to be summarized through 30 days post dose and stage 2 analysis safety summarised through 90 days post dose and through end of the study. Primary analysis population changed from Intent-to-treat to modified Intent-to-treat population. Stratification factors for country and prior systemic antibiotics not to be included in the analysis model. Further clarification regarding the analysis was also added Secondary efficacy analysis section was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported