Clinical trial results:
A CONFIRMATORY PHASE II/III STUDY ASSESSING EFFICACY, IMMUNOGENICITY AND SAFETY OF IC43 RECOMBINANT PSEUDOMONAS VACCINE IN INTENSIVE CARE PATIENTS.

Summary

EudraCT number	2011-004771-36
Trial protocol	AT DE HU ES BE CZ
Global end of trial date	29 December 2015

Results information

Result version number	v1 (current)
This version publication date	09 February 2017
First version publication date	09 February 2017

Trial information

Trial identification

Sponsor protocol code	IC43-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01563263
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Valneva Austria GmbH
Sponsor organisation address	Campus Vienna Biocenter 3, Vienna, Austria, 1030
Public contact	Clinical Operations, Valneva Austria GmbH, 0043 1206200, info@valneva.com
Scientific contact	Clinical Operations, Valneva Austria GmbH, 0043 1206200, info@valneva.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	04 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show the superiority of IC43 with regard to overall mortality on Day 28 after first vaccination in mechanically ventilated ICU patients.

Protection of trial subjects:

An independent DMC was established to review safety data in the course of the futility analysis (i.e., after approximately 50% of patients had been enrolled) and recommended on continuation/ modification/ discontinuation of the study in case of safety concerns. In addition, the DMC reviewed the Day-28 mortality data in the course of the futility analysis and informed the sponsor of futility of IC43 in case the predefined futility criterion was met. The sponsor, investigator and any person involved in the study remained blinded.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2012
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	Spain: 113
Country: Number of subjects enrolled	Austria: 170
Country: Number of subjects enrolled	Belgium: 233
Country: Number of subjects enrolled	Czech Republic: 43
Country: Number of subjects enrolled	Germany: 112
Country: Number of subjects enrolled	Hungary: 128
Worldwide total number of subjects	799
EEA total number of subjects	799

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)	426
From 65 to 84 years	371
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Recruitment started in March 2012 and for the first part of the study (i.e. prior to the planned futility analysis) was completed in July 2013. Following the futility analysis, recruitment was resumed in June 2014, the last patient was enrolled in study IC43-202 beginning of July 2015.

Pre-assignment

Screening details:

Male and female patients aged 18 to 80 years admitted to an Intensive Care Unit (ICU) with the need for mechanical ventilation (>48 hours) were screened for study participation. The study aimed for enrollment of medical patients, patients admitted to ICU within 2 days after surgery or due to trauma were not eligible for participation.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	IC43

Arm description:

2 vaccinations, administered 7 days apart

Arm type	Experimental
Investigational medicinal product name	IC43
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The final protein concentration was 100 µg/mL. 1ml was injected per vaccination.

Arm title	Placebo

Arm description:

2 vaccinations, administered 7 days apart

Arm type	Placebo
Investigational medicinal product name	phosphate buffered saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo consisted of PBS solution containing 0.9% NaCl. 1ml was injected per vaccination.

Number of subjects in period 1	IC43	Placebo
Started	393	406
Completed	175	203
Not completed	218	203
relative withdrew consent	-	1
Consent withdrawn by subject	10	9
Physician decision	3	-
family withdrew consent	1	-
patient not reached for visit 5 but known alive	1	-
transferred to another hospital	-	2
Adverse event, non-fatal	-	1
Death	172	166
Lost to follow-up	28	24
transfer to other hospital	1	-
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	IC43
Reporting group description:	
2 vaccinations, administered 7 days apart	
Reporting group title	Placebo
Reporting group description:	
2 vaccinations, administered 7 days apart	

Reporting group values	IC43	Placebo	Total
Number of subjects	393	406	799
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	61.9	62	
standard deviation	± 12.57	± 11.88	-
Gender categorical			
Units: Subjects			
Female	130	134	264
Male	263	272	535
SOFA score at study entry			
SOFA = sequential organ failure assessment			
Units: score			
arithmetic mean	8.1	8.2	
standard deviation	± 2.9	± 2.8	-

End points

End points reporting groups	
Reporting group title	IC43
Reporting group description: 2 vaccinations, administered 7 days apart	
Reporting group title	Placebo
Reporting group description: 2 vaccinations, administered 7 days apart	

Primary: all-cause mortality at Day 28	
End point title	all-cause mortality at Day 28
End point description: percentages are based on the number of non-missing observations	
End point type	Primary
End point timeframe: at Day 28 = 28 days after first study vaccination	

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	406		
Units: percent				
number (confidence interval 95%)	29.2 (24.8 to 34)	27.7 (23.5 to 32.3)		

Statistical analyses

Statistical analysis title	CMH test stratified for pooled country
Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.674
Method	Cochran-Mantel-Haenszel

Secondary: all-cause mortality in all patients	
End point title	all-cause mortality in all patients

End point description: percentages are based on the number of non-missing observations	
End point type	Secondary
End point timeframe: mortality rate at Day 14, 56 and 90 after first vaccination	

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	406		
Units: percent				
number (confidence interval 95%)				
all-cause mortality at Day 14	17.1 (13.7 to 21.2)	19.8 (16.2 to 24)		
all-cause mortality at Day 56	37.6 (32.7 to 42.7)	38.9 (34.2 to 43.9)		
all-cause mortality at Day 90	44.4 (39.2 to 49.6)	42.7 (37.8 to 47.8)		

Statistical analyses

Statistical analysis title	CMH test stratified for pooled country (Day 14)
Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5152
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test stratified for pooled country (Day 56)
Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8251
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test stratified for pooled country (Day 90)

Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6073
Method	Cochran-Mantel-Haenszel

Secondary: all-cause mortality in all patients surviving Day 14	
End point title	all-cause mortality in all patients surviving Day 14
End point description: percentages are based on the number of non-missing observations	
End point type	Secondary
End point timeframe: mortality rate at Day 28, 56 and 90 after first vaccination	

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: percent				
number (confidence interval 95%)				
mortality on Day 28 in patients surviving Day 14	15.5 (11.9 to 19.9)	10.5 (7.6 to 14.4)		
mortality on Day 56 in patients surviving Day 14	25.1 (20.5 to 30.3)	24.1 (19.7 to 29.2)		
mortality on Day 90 in patients surviving Day 14	32.8 (27.6 to 38.4)	28.2 (23.4 to 33.6)		

Statistical analyses

Statistical analysis title	CMH test stratified for pooled country (Day 28)
Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1493
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test stratified for pooled country (Day 56)

Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8847
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test stratified for pooled country (Day 90)
Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3148
Method	Cochran-Mantel-Haenszel

Secondary: all-cause mortality in all patients surviving Day 3	
End point title	all-cause mortality in all patients surviving Day 3
End point description: percentages are based on the number of non-missing observations	
End point type	Secondary
End point timeframe: mortality rate at Day 14, 28, 56 and 90 after first vaccination	

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	389		
Units: percent				
number (confidence interval 95%)				
mortality at Day 14 in patients surviving Day 3	13.2 (10.1 to 17.1)	17.5 (14.1 to 21.7)		
mortality at Day 28 in patients surviving Day 3	25.8 (21.5 to 30.6)	25.7 (21.5 to 30.3)		
mortality at Day 56 in patients surviving Day 3	34.5 (29.7 to 39.7)	37.2 (32.4 to 42.2)		
mortality at Day 90 in patients surviving Day 3	41.5 (36.3 to 46.9)	41.1 (36.1 to 46.2)		

Statistical analyses

Statistical analysis title	CMH test stratified for pooled country (Day 14)
Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2173
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test stratified for pooled country (Day 28)
Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.968
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test stratified for pooled country (Day 56)
Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5712
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test stratified for pooled country (Day 90)
Statistical analysis description: CMH test = Cochran-Mantel-Haenszel test	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8143
Method	Cochran-Mantel-Haenszel

Secondary: survival estimates (survival rate) in all patients	
End point title	survival estimates (survival rate) in all patients
End point description: Kaplan-Meier survival estimates for all patients	
End point type	Secondary
End point timeframe: survival estimates on Day 14, 28, 56, 90 and Day 180	

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	404		
Units: percent				
number (confidence interval 95%)				
Day 14	83.1 (79 to 86.5)	80.4 (76.1 to 84)		
Day 28	71.5 (66.6 to 75.8)	72.6 (68 to 76.8)		
Day 56	63.9 (58.7 to 68.5)	61.9 (56.8 to 66.5)		
Day 90	58.2 (52.9 to 63.1)	59.4 (54.3 to 64.4)		
Day 180	53 (47.7 to 58)	57.4 (52.3 to 62.2)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4603
Method	Logrank

Secondary: overall survival in patients surviving Day 14	
End point title	overall survival in patients surviving Day 14
End point description: Kaplan-Meier survival estimate for patients surviving Day 14	
End point type	Secondary
End point timeframe: overall survival	

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: percent censored				
number (not applicable)	65.31	71.7		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0573
Method	Logrank

Secondary: percentage of patients with P. aeruginosa infection that started up to a certain time point (confirmed by DMC and assessed by investigator)

End point title	percentage of patients with P. aeruginosa infection that started up to a certain time point (confirmed by DMC and assessed by investigator)

End point description:

percentage of patients with at least one invasive P. aeruginosa infection (bacteremia or urinary tract infection), with at least one P. aeruginosa respiratory tract infection (pneumonia or tracheobronchitis), or with at least one P. aeruginosa respiratory tract colonization.
As confirmed by DMC (Data Monitoring Committee) and as assessed by investigator.

End point type	Secondary

End point timeframe:

infections that started up to Day 28, 56, 90 and 180, respectively, including infections prevalent at baseline

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	406		
Units: percent				
number (confidence interval 95%)				
invasive, up to Day 28, DMC	2.3 (1.2 to 4.3)	3 (1.7 to 5.1)		
invasive, up to Day 28, investigator	5.6 (3.7 to 8.3)	5.4 (3.6 to 8.1)		
respiratory tract, up to Day 28, DMC	9.7 (7.1 to 13)	11.3 (8.6 to 14.8)		
respiratory tract, up to Day 28, investigator	12.5 (9.6 to 16.1)	13.1 (10.1 to 16.7)		
colonization, up to Day 28, DMC	9.9 (7.3 to 13.3)	5.7 (3.8 to 8.4)		
colonization, up to Day 28, investigator	9.2 (6.7 to 12.4)	4.9 (3.2 to 7.5)		

invasive, up to Day 56, DMC	2.5 (1.4 to 4.6)	3.4 (2.1 to 5.7)		
invasive, up to Day 56, investigator	8.9 (6.5 to 12.1)	7.1 (5 to 10.1)		
respiratory tract, up to Day 56, DMC	10.7 (8 to 14.1)	13.1 (10.1 to 16.7)		
respiratory tract, up to Day 56, investigator	14.2 (11.1 to 18.1)	15.3 (12.1 to 19.1)		
colonization, up to Day 56, DMC	11.7 (8.9 to 15.3)	6.7 (4.6 to 9.5)		
colonization, up to Day 56, investigator	10.4 (7.8 to 13.8)	5.4 (3.6 to 8.1)		
invasive, up to Day 90, DMC	2.8 (1.6 to 4.9)	3.7 (2.3 to 6)		
invasive, up to Day 90, investigator	9.7 (7.1 to 13)	8.1 (5.8 to 11.2)		
respiratory tract, up to Day 90, DMC	11.7 (8.9 to 15.3)	13.1 (10.1 to 16.7)		
respiratory tract, up to Day 90, investigator	15.3 (12 to 19.2)	15.5 (12.3 to 19.4)		
colonization, up to Day 90, DMC	12.2 (9.3 to 15.8)	6.9 (4.8 to 9.8)		
colonization, up to Day 90, investigator	10.9 (8.2 to 14.4)	5.7 (3.8 to 8.4)		
invasive, up to Day 180, DMC	3.3 (1.9 to 5.6)	4.2 (2.6 to 6.6)		
invasive, up to Day 180, investigator	10.7 (8 to 14.1)	8.9 (6.5 to 12)		
respiratory tract, up to Day 180, DMC	12 (9.1 to 15.5)	13.1 (10.1 to 16.7)		
respiratory tract, up to Day 180, investigator	15.5 (12.3 to 19.4)	15.8 (12.5 to 19.6)		
colonization, up to Day 180, DMC	12.2 (9.3 to 15.8)	7.4 (5.2 to 10.4)		
colonization, up to Day 180, investigator	10.9 (8.2 to 14.4)	5.9 (4 to 8.6)		

Statistical analyses

Statistical analysis title	CMH test, invasive, up to Day 28, DMC

Statistical analysis description:

P. aeruginosa invasive infections that started up to Day 28: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3753
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, invasive, up to Day 28, investigator

Statistical analysis description:

P. aeruginosa invasive infections that started up to Day 28: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator

Comparison groups	IC43 v Placebo

Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9072
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, resp. tract, up to Day 28, DMC
Statistical analysis description:	
P. aeruginosa respiratory tract infections that started up to Day 28: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4948
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, resp. tract, up to Day 28, investigator
Statistical analysis description:	
P. aeruginosa respiratory tract infections that started up to Day 28: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4716
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, colonization, up to Day 28, DMC
Statistical analysis description:	
P. aeruginosa respiratory tract colonizations that started up to Day 28: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, colonization, up to Day 28, investigator
Statistical analysis description:	
P. aeruginosa respiratory tract colonizations that started up to Day 28: Cochran-Mantel-Haenszel test	

stratified for pooled country - assessed by investigator

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0067
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, invasive, up to Day 56, DMC

Statistical analysis description:

P. aeruginosa invasive infections that started up to Day 56: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3477
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, invasive, up to Day 56, investigator

Statistical analysis description:

P. aeruginosa invasive infections that started up to Day 56: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4097
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, resp. tract, up to Day 56, DMC

Statistical analysis description:

P. aeruginosa respiratory tract infections that started up to Day 56: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3635
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, resp. tract, up to Day 56, investigator

Statistical analysis description:	
P. aeruginosa respiratory tract infections that started up to Day 56: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3129
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, colonization, up to Day 56, DMC
Statistical analysis description:	
P. aeruginosa respiratory tract colonizations that started up to Day 56: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC	
Comparison groups	Placebo v IC43
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0258
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, colonization, up to Day 56, investigator
Statistical analysis description:	
P. aeruginosa respiratory tract colonizations that started up to Day 56: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, invasive, up to Day 90, DMC
Statistical analysis description:	
P. aeruginosa invasive infections that started up to Day 90: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.447
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, invasive, up to Day 90, investigator
Statistical analysis description:	
P. aeruginosa invasive infections that started up to Day 90: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4492
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, resp. tract, up to Day 90, DMC
Statistical analysis description:	
P. aeruginosa respiratory tract infections that started up to Day 90: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7136
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, resp. tract, up to Day 90, investigator
Statistical analysis description:	
P. aeruginosa respiratory tract infections that started up to Day 90: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5537
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, colonization, up to Day 90, DMC
Statistical analysis description:	
P. aeruginosa respiratory tract colonizations that started up to Day 90: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, colonization, up to Day 90, investigator
Statistical analysis description:	
P. aeruginosa respiratory tract colonizations that started up to Day 90: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, invasive, up to Day 180, DMC
Statistical analysis description:	
P. aeruginosa invasive infections that started up to Day 180: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8681
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, invasive, up to Day 180, investigator
Statistical analysis description:	
P. aeruginosa invasive infections that started up to Day 180: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2219
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, resp. tract, up to Day 180, DMC
Statistical analysis description:	
P. aeruginosa respiratory tract infections that started up to Day 180: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC	
Comparison groups	IC43 v Placebo

Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9852
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, resp. tract, up to Day 180, investigator

Statistical analysis description:

P. aeruginosa respiratory tract infections that started up to Day 180: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6054
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, colonization, up to Day 180, DMC

Statistical analysis description:

P. aeruginosa respiratory tract colonizations that started up to Day 180: Cochran-Mantel-Haenszel test stratified for pooled country - confirmed by DMC

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0371
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CMH test, colonization, up to Day 180,investigator

Statistical analysis description:

P. aeruginosa respiratory tract colonizations that started up to Day 180: Cochran-Mantel-Haenszel test stratified for pooled country - assessed by investigator

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0052
Method	Cochran-Mantel-Haenszel

Secondary: GMT for OprF/I specific antibodies

End point title	GMT for OprF/I specific antibodies

End point description:

GMT = geometric mean titer

End point type	Secondary

End point timeframe:

GMT for OprF/I specific antibodies on Day 0, 7, 14, 28, 56 and 180

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	406		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Day 0	129.4 (120.5 to 138.8)	136 (125.8 to 146.9)		
Day 7	198.1 (175.8 to 223.3)	144.2 (132.4 to 157.1)		
Day 14	1804.6 (1425.3 to 2284.9)	156.3 (140.4 to 174.1)		
Day 28	2592.4 (1997.8 to 3364.1)	163.9 (144.3 to 186.1)		
Day 56	1143.3 (864.8 to 1511.4)	169.7 (143.7 to 200.4)		
Day 180	425.2 (307.9 to 587.2)	157.9 (129.7 to 192.3)		

Statistical analyses

Statistical analysis title	ANOVA at Day 0

Statistical analysis description:

ANOVA = analysis of variance
ANOVE (factors: pooled country, treatment group) for geometric mean of absolute values of OprF/I specific antibodies

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3638
Method	ANOVA

Statistical analysis title	ANOVA at Day 7

Statistical analysis description:

ANOVA = analysis of variance
ANOVE (factors: pooled country, treatment group) for geometric mean of absolute values of OprF/I specific antibodies

Comparison groups	IC43 v Placebo

Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA

Statistical analysis title	ANOVA at Day 14

Statistical analysis description:

ANOVA = analysis of variance
ANOVE (factors: pooled country, treatment group) for geometric mean of absolute values of OprF/I specific antibodies

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA

Statistical analysis title	ANOVA at Day 28

Statistical analysis description:

ANOVA = analysis of variance
ANOVE (factors: pooled country, treatment group) for geometric mean of absolute values of OprF/I specific antibodies

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA

Statistical analysis title	ANOVA at Day 56

Statistical analysis description:

ANOVA = analysis of variance
ANOVE (factors: pooled country, treatment group) for geometric mean of absolute values of OprF/I specific antibodies

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA

Statistical analysis title	ANOVA at Day 180

Statistical analysis description:
ANOVA = analysis of variance ANOVE (factors: pooled country, treatment group) for geometric mean of absolute values of OprF/I specific antibodies

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA

Secondary: percentage of patients experiencing any AE up to Day 180

End point title	percentage of patients experiencing any AE up to Day 180

End point description:
AE = adverse event

End point type	Secondary

End point timeframe:
up to Day 180 = up to 180 days after first study vaccination

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	403		
Units: percent				
number (confidence interval 95%)	93.1 (90.2 to 95.2)	96.5 (94.3 to 97.9)		

Statistical analyses

Statistical analysis title	Fisher's exact test

Statistical analysis description:
Fisher's exact test (based on N)

Comparison groups	IC43 v Placebo
Number of subjects included in analysis	796
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0365
Method	Fisher exact

Secondary: percentage of patients experiencing an SAE up to Day 180

End point title	percentage of patients experiencing an SAE up to Day 180

End point description:
SAE = serious adverse event

End point type	Secondary
End point timeframe: up to Day 180 = up to 180 days after first study vaccination	

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	403		
Units: percent				
number (confidence interval 95%)	57.8 (52.8 to 62.5)	57.6 (52.7 to 62.3)		

Statistical analyses

Statistical analysis title	Fisher's exact test
Statistical analysis description: Fisher's exact test (based on N)	
Comparison groups	IC43 v Placebo
Number of subjects included in analysis	796
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Systemic tolerability: percentage of patients with any abnormalities in vital signs (pulse, blood pressure) within 1 hour after vaccination

End point title	Systemic tolerability: percentage of patients with any abnormalities in vital signs (pulse, blood pressure) within 1 hour after vaccination
End point description: Percentages are based on the number of non-missing observations within each stratum (Total)	
End point type	Secondary
End point timeframe: at Day 0 (first vaccination) and at Day 7 (second vaccination)	

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	403		
Units: percent				
number (confidence interval 95%)				
Day 0	0.8 (0.3 to 2.2)	0.7 (0.3 to 2.2)		
Day 7	0.3 (0.1 to 1.6)	0 (0 to 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: presence of local tolerability of injection site of first vaccination at Day 0 and Day 7 and of second vaccination at Day 7 and Day 14

End point title	presence of local tolerability of injection site of first vaccination at Day 0 and Day 7 and of second vaccination at Day 7 and Day 14

End point description:

Evaluation of erythema/redness, induration, itching, pain, swelling, tenderness.

Percentages are based on the number of non-missing observations within each stratum (Total).

End point type	Secondary

End point timeframe:

first vaccination: evaluation 60 min after vaccination at Day 0 and inspection and evaluation on Day 7. second vaccination: evaluation 60 min after vaccination at Day 7 and inspection and evaluation on Day 14.

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	403		
Units: percent				
number (confidence interval 95%)				
first, Day 0, erythema/redness	0.3 (0 to 1.4)	0 (0 to 0.9)		
first, Day 7, erythema/redness	0.6 (0.2 to 2)	0 (0 to 1.1)		
first, Day 0, induration	0.5 (0.1 to 1.8)	0.2 (0 to 1.4)		
first, Day 7, induration	0.6 (0.2 to 2)	0.6 (0.2 to 2)		
first, Day 0, itching	0 (0 to 1)	0 (0 to 0.9)		
first, Day 7, itching	0 (0 to 1.1)	0 (0 to 1.1)		
first, Day 0, pain	0 (0 to 1)	0.2 (0 to 1.4)		
first, Day 7, pain	0.3 (0.1 to 1.6)	0.6 (0.2 to 2)		
first, Day 0, swelling	0.3 (0 to 1.4)	0 (0 to 0.9)		
first, Day 7, swelling	0 (0 to 1.1)	0.3 (0 to 1.6)		
first, Day 0, tenderness	0 (0 to 1)	0 (0 to 0.9)		
first, Day 7, tenderness	0 (0 to 1.1)	0 (0 to 1.1)		
second, Day 7, erythema/redness	0.3 (0.1 to 1.6)	0 (0 to 1.1)		
second, Day 14, erythema/redness	0.3 (0.1 to 1.8)	1 (0.3 to 2.9)		
second, Day 7, induration	0.9 (0.3 to 2.5)	0.3 (0.1 to 1.6)		
second, Day 14, induration	1.3 (0.5 to 3.2)	1 (0.3 to 2.9)		
second, Day 7, itching	0 (0 to 1.1)	0 (0 to 1.1)		
second, Day 14, itching	0 (0 to 1.2)	0 (0 to 1.2)		
second, Day 7, pain	0 (0 to 1.1)	0.3 (0.1 to 1.6)		
second, Day 14, pain	0 (0 to 1.2)	0 (0 to 1.2)		

second, Day 7, swelling	0 (0 to 1.1)	0 (0 to 1.1)		
second, Day 14, swelling	0 (0 to 1.2)	1 (0.3 to 2.9)		
second, Day 7, tenderness	0 (0 to 1.1)	0.3 (0.1 to 1.6)		
second, Day 14, tenderness	0 (0 to 1.2)	0.3 (0.1 to 1.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic tolerability: percentage of patients with any new abnormalties or any worsening in intensity or frequency of a pre-existing condition during or within 1 hour after vaccination

End point title	Systemic tolerability: percentage of patients with any new abnormalties or any worsening in intensity or frequency of a pre-existing condition during or within 1 hour after vaccination
End point description:	
Percentages are based on the number of non-missing observations within each stratum (Total)	
End point type	Secondary
End point timeframe:	
at Day 0 (first vaccination) and at Day 7 (second vaccination)	

End point values	IC43	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	403		
Units: percent				
number (confidence interval 95%)				
Day 0	0 (0 to 1)	1 (0.4 to 2.5)		
Day 7	0.3 (0.1 to 1.6)	0 (0 to 1.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were collected throughout the study, i.e., up to 6 months after first vaccination	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	IC43
Reporting group description: 2 vaccinations, administered 7 days apart	
Reporting group title	Placebo
Reporting group description: 2 vaccinations, administered 7 days apart	

Serious adverse events	IC43	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	227 / 393 (57.76%)	232 / 403 (57.57%)	
number of deaths (all causes)	173	166	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoid tumour pulmonary			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon adenoma			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hairy cell leukaemia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung neoplasm malignant			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Plasma cell myeloma			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive crisis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 393 (0.76%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	2 / 393 (0.51%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	4 / 393 (1.02%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Surgical and medical procedures			
Tracheostomy			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Brain death			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac death			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Condition aggravated			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Death			
subjects affected / exposed	7 / 393 (1.78%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 7	0 / 1	

Device occlusion			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 393 (0.76%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Impaired healing			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ disorder			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multi-organ failure			
subjects affected / exposed	17 / 393 (4.33%)	21 / 403 (5.21%)	
occurrences causally related to treatment / all	0 / 17	0 / 21	
deaths causally related to treatment / all	0 / 16	0 / 21	
Pyrexia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory distress syndrome			
subjects affected / exposed	5 / 393 (1.27%)	5 / 403 (1.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 4	
Acute respiratory failure			
subjects affected / exposed	2 / 393 (0.51%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Apnoea			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asphyxia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	1 / 393 (0.25%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchospasm			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 393 (0.76%)	3 / 403 (0.74%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	3 / 393 (0.76%)	3 / 403 (0.74%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	2 / 393 (0.51%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infiltration			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oropharyngeal spasm			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 393 (0.51%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 393 (0.51%)	5 / 403 (1.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pulmonary fibrosis			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			

subjects affected / exposed	2 / 393 (0.51%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory disorder			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	2 / 393 (0.51%)	3 / 403 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	29 / 393 (7.38%)	28 / 403 (6.95%)	
occurrences causally related to treatment / all	0 / 30	1 / 32	
deaths causally related to treatment / all	0 / 21	0 / 14	
Respiratory fatigue			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restrictive pulmonary disease			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stridor			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal stenosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Delayed haemolytic transfusion reaction			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Facial bones fracture			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripancreatic fluid collection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt malfunction			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt occlusion			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 393 (0.25%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 1	
Angina pectoris			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	17 / 393 (4.33%)	20 / 403 (4.96%)	
occurrences causally related to treatment / all	0 / 17	0 / 20	
deaths causally related to treatment / all	0 / 15	0 / 16	
Cardiac disorder			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	15 / 393 (3.82%)	5 / 403 (1.24%)	
occurrences causally related to treatment / all	0 / 16	0 / 5	
deaths causally related to treatment / all	0 / 12	0 / 5	
Cardiac failure acute			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	2 / 393 (0.51%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 393 (0.25%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiogenic shock			

subjects affected / exposed	3 / 393 (0.76%)	3 / 403 (0.74%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 2	
Cardiopulmonary failure			
subjects affected / exposed	12 / 393 (3.05%)	10 / 403 (2.48%)	
occurrences causally related to treatment / all	0 / 12	0 / 10	
deaths causally related to treatment / all	0 / 12	0 / 10	
Cardiovascular insufficiency			
subjects affected / exposed	2 / 393 (0.51%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Chordae tendinae rupture			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor pulmonale acute			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	3 / 393 (0.76%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tachyarrhythmia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain hypoxia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain injury			
subjects affected / exposed	4 / 393 (1.02%)	4 / 403 (0.99%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 4	
Brain oedema			

subjects affected / exposed	3 / 393 (0.76%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cerebellar infarction			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery occlusion			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	0 / 393 (0.00%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cerebral infarction			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	2 / 393 (0.51%)	3 / 403 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Cerebrovascular accident			
subjects affected / exposed	1 / 393 (0.25%)	4 / 403 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 4	
Coma			
subjects affected / exposed	4 / 393 (1.02%)	4 / 403 (0.99%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 3	
Critical illness polyneuropathy			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hemiparesis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	2 / 393 (0.51%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	2 / 393 (0.51%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Intraventricular haemorrhage			

subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuroleptic malignant syndrome			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Polyneuropathy			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 393 (0.51%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Syncope			

subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal compartment syndrome			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal discomfort			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enteritis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	2 / 393 (0.51%)	4 / 403 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileus			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Megacolon			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 393 (0.25%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			

subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic necrosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 393 (0.51%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngo-oesophageal diverticulum			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			

subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 393 (0.51%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 393 (0.00%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic cirrhosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	3 / 393 (0.76%)	4 / 403 (0.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Calculus urinary			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 393 (0.76%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Appendicitis perforated			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain abscess			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	2 / 393 (0.51%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 393 (0.25%)	3 / 403 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Escherichia sepsis			

subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Influenza			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Meningoencephalitis bacterial			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic abscess			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	12 / 393 (3.05%)	9 / 403 (2.23%)	
occurrences causally related to treatment / all	0 / 12	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Pneumonia necrotising			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia pseudomonal			
subjects affected / exposed	5 / 393 (1.27%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary sepsis			
subjects affected / exposed	0 / 393 (0.00%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Retroperitoneal abscess			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	13 / 393 (3.31%)	10 / 403 (2.48%)	
occurrences causally related to treatment / all	0 / 14	0 / 10	
deaths causally related to treatment / all	0 / 9	0 / 4	
Septic shock			

subjects affected / exposed	11 / 393 (2.80%)	21 / 403 (5.21%)	
occurrences causally related to treatment / all	0 / 11	0 / 21	
deaths causally related to treatment / all	0 / 9	0 / 18	
Soft tissue infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 393 (0.25%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 393 (0.25%)	2 / 403 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoglycaemia			

subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 393 (0.00%)	1 / 403 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolic disorder			
subjects affected / exposed	1 / 393 (0.25%)	0 / 403 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IC43	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	339 / 393 (86.26%)	365 / 403 (90.57%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 393 (5.09%)	29 / 403 (7.20%)	
occurrences (all)	20	31	
Hypotension			
subjects affected / exposed	21 / 393 (5.34%)	27 / 403 (6.70%)	
occurrences (all)	22	27	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	28 / 393 (7.12%)	22 / 403 (5.46%)	
occurrences (all)	32	23	
Nervous system disorders			
Critical illness polyneuropathy			
subjects affected / exposed	20 / 393 (5.09%)	14 / 403 (3.47%)	
occurrences (all)	20	14	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	42 / 393 (10.69%)	62 / 403 (15.38%)	
occurrences (all)	56	78	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	38 / 393 (9.67%)	40 / 403 (9.93%)	
occurrences (all)	38	42	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	57 / 393 (14.50%)	52 / 403 (12.90%)	
occurrences (all)	65	60	
Vomiting			
subjects affected / exposed	23 / 393 (5.85%)	23 / 403 (5.71%)	
occurrences (all)	25	27	
Constipation			
subjects affected / exposed	21 / 393 (5.34%)	22 / 403 (5.46%)	
occurrences (all)	21	22	
Impaired gastric emptying			
subjects affected / exposed	18 / 393 (4.58%)	24 / 403 (5.96%)	
occurrences (all)	19	24	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	28 / 393 (7.12%)	30 / 403 (7.44%)	
occurrences (all)	28	33	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	53 / 393 (13.49%)	49 / 403 (12.16%)	
occurrences (all)	56	55	
Psychiatric disorders			
Agitation			
subjects affected / exposed	31 / 393 (7.89%)	38 / 403 (9.43%)	
occurrences (all)	32	39	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	52 / 393 (13.23%)	51 / 403 (12.66%)	
occurrences (all)	62	55	
Pneumonia			

subjects affected / exposed	35 / 393 (8.91%)	43 / 403 (10.67%)	
occurrences (all)	41	46	
Tracheobronchitis			
subjects affected / exposed	28 / 393 (7.12%)	32 / 403 (7.94%)	
occurrences (all)	33	35	
Bacterial disease carrier			
subjects affected / exposed	24 / 393 (6.11%)	17 / 403 (4.22%)	
occurrences (all)	36	22	
Sepsis			
subjects affected / exposed	21 / 393 (5.34%)	20 / 403 (4.96%)	
occurrences (all)	23	20	
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	17 / 393 (4.33%)	24 / 403 (5.96%)	
occurrences (all)	18	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2012	1. Update of secondary efficacy endpoints to correctly reflect the description of statistical analysis as per section 10.4 of the study protocol. 2. Table Of Events: no changes in content but activities were re-arranged to largely reflect chronological order of tasks to be performed at each study visit. 3. To include the option of having a serum pregnancy test performed in female patients of childbearing potential instead of a urine pregnancy test. 4. To describe more precisely assessment of SOFA and APACHE II scores. 5. Definition of acceptable methods of birth control in line with the Informed Consent Form. 6. To correctly present the pre-defined futility criterion and operational characteristics of the interim analysis including unconditional power, significance level and conditional power for the planned (unchanged) sample size. 7. To add editorial changes.
16 May 2014	Revision of section 2.2 "Secondary Objectives" to include analysis of overall mortality on Day 28 and overall survival in ventilated ICU patients with documented medical history of a hepatobiliary disorder. Revision of section 3.1.2 "Secondary Endpoints" to include secondary endpoints regarding overall mortality on Day 28 and overall survival in ventilated ICU patients with documented medical history of a hepatobiliary disorder. Update of section 3.2.1 "Overall design and control method" to include justification for introduction of new secondary endpoints and objectives. Revision of sections 5.1.2 "Packaging & labeling of IC43" and 5.2.2 "5.2.2 Packaging & labeling of placebo" to reflect the address change of ABF Revision of section 10.4 "Secondary Efficacy Analysis" to include stratification of survival endpoints and mortality rate for the presence of any hepatobiliary disorder in the patient's Medical History;

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported