

## **A PHASE 2 PILOT STUDY ASSESSING IMMUNOGENICITY AND SAFETY OF IC43 IN INTENSIVE CARE PATIENTS**

Protocol Number: IC43-201  
EudraCT number: 2008-005037-30  
ClinicalTrials.gov id: NCT00876252

Sponsor: Valneva Austria GmbH (previously Intercell AG, Austria)

Name of Investigational Product: IC43 (Pseudomonas aeruginosa vaccine)

### **Overall Study Design and Plan**

This was a randomized, placebo-controlled, multi-center, partially-blinded (blinded for adjuvanted IC43 [i.e., 100 mcg and 200 mcg IC43 with Al(OH)<sub>3</sub>, respectively] and placebo, but unblinded for non-adjuvanted IC43 [i.e., 100 mcg w/o Al(OH)<sub>3</sub>]) phase 2 pilot study. The study population consisted of male or female intensive care unit (ICU) patients aged between 18 and 80 years, with a need for mechanical ventilation for more than 48 hours.

A total of 400 patients was planned to be enrolled at approximately 50 study centers and randomized in four groups receiving different dosages and formulations of IC43 or placebo.

Patients received either 2 injections (groups "200 mcg with Al(OH)<sub>3</sub>", "100 mcg with Al(OH)<sub>3</sub>", "placebo") or 1 injection (group "100 mcg w/o Al(OH)<sub>3</sub>") at each vaccination visit (day 0, day 7) via the intramuscular route in the deltoid region of one upper arm. According to the group the patients have been allocated, they received the following injections:

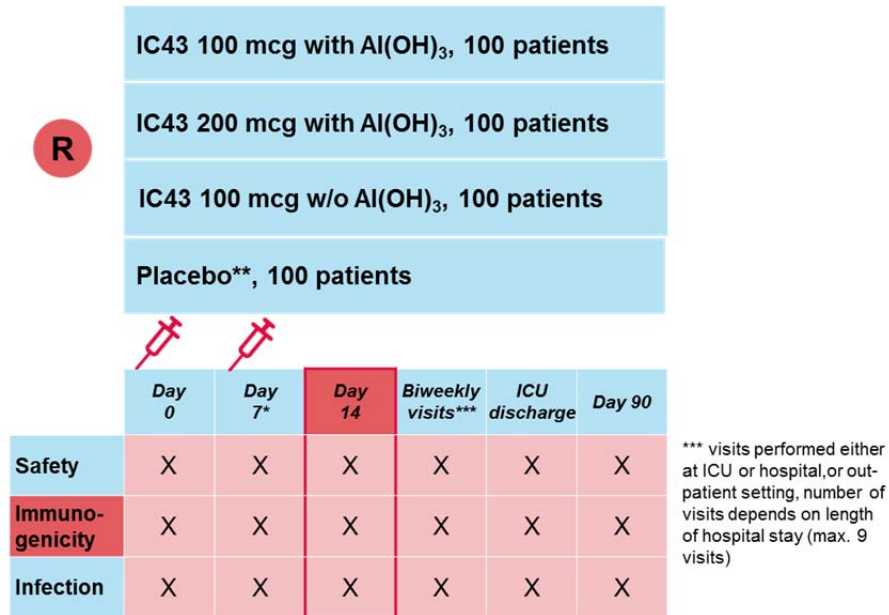
- 100 mcg with Al(OH)<sub>3</sub>: 1 ml of IC43 with Al(OH)<sub>3</sub> and 1 ml of placebo with Al(OH)<sub>3</sub> (one syringe filled with 1 ml of IC43 with Al(OH)<sub>3</sub>, one syringe filled with 1 ml of placebo with Al(OH)<sub>3</sub>)
- 200 mcg with Al(OH)<sub>3</sub>: 2 x 1 ml of IC43 with Al(OH)<sub>3</sub> (two syringes filled with 1 ml of IC43 with Al(OH)<sub>3</sub>, respectively)
- Placebo: 2 x 1 ml of placebo with Al(OH)<sub>3</sub> (two syringes filled with 1 ml of placebo with Al(OH)<sub>3</sub>, respectively)
- 100 mcg w/o Al(OH)<sub>3</sub>: 1 ml of IC43 without Al(OH)<sub>3</sub> (one syringe filled with 1 ml of IC43 without Al(OH)<sub>3</sub>)

Surveillance and blood cultures were obtained at regular intervals during ICU stay to identify any invasive infection and colonization with *P. aeruginosa*. Cultures from blood, respiratory secretions, wound, urine or central venous catheters were additionally collected as medically indicated at the investigator's discretion during ICU and hospital stay.

Each patient participated in the study for a maximum of 9 visits (Days 0, 7, 14, 28, 42, 56, 70 and 90) over a period of 90 days:

- Treatment period: up to 7 days (vaccinations on Days 0 and 7)
- Follow-up period: max. until day 90

## Study Design



## Number Patients per Analysis Population

	IC43 100 mcg (N=104) No. (%)	IC43 100 mcg w/o (N=98) No. (%)	IC43 200 mcg (N=101) No. (%)	Placebo (N=98) No. (%)	Not randomized (N=7) No. (%)	Randomized (N=401) No. (%)
ITT population	104 (100)	98 (100)	101 (100)	98 (100)	0 (0.0)	401 (100)
PP Population	87 (83.7)	73 (74.5)	77 (76.2)	77 (78.6)	0 (0.0)	314 (78.3)
Safety Population	104 (100)	98 (100)	101 (100)	98 (100)	0 (0.0)	401 (100)

## Reasons for Discontinuation (ITT population)

	IC43 100 mcg (N=53) No. (%)	IC43 100 mcg w/o (N=45) No. (%)	IC43 200 mcg (N=49) No. (%)	Placebo (N=56) No. (%)
Drop-Out reason				
Patient withdrew consent	4 (7.5)	4 (8.9)	6 (12.2)	4 (7.1)
Death	37 (69.8)	27 (60.0)	38 (77.6)	42 (75.0)
Lost to follow-up	9 (17.0)	13 (28.9)	5 (10.2)	7 (12.5)
Other reason	3 (5.7)	1 (2.2)	0 (0.0)	3 (5.4)
Total	53	45	49	56

**Location of vaccination (arm) by visit and group (Safety population)**

<b>Vaccination</b>		<b>IC43 100 mcg (N=104) No. (%)</b>	<b>IC43 100 mcg w/o (N=98) No. (%)</b>	<b>IC43 200 mcg (N=101) No. (%)</b>	<b>Placebo (N=98) No. (%)</b>	<b>Total (N=401) No. (%)</b>
<b>1<sup>st</sup> vaccination</b>	Location					
	right arm	56 (53.8)	57 (58.2)	56 (55.4)	53 (54.1)	222 (55.4)
	left arm	48 (46.2)	41 (41.8)	45 (44.6)	45 (45.9)	179 (44.6)
	Total	104	98	101	98	401
<b>2<sup>nd</sup> vaccination</b>	Location					
	right arm	48 (50.5)	47 (54.0)	47 (52.8)	48 (58.5)	190 (53.8)
	left arm	47 (49.5)	40 (46.0)	42 (47.2)	34 (41.5)	163 (46.2)
	Total	95	87	89	82	353
Percentages are based on the number of non-missing observations within each stratum (Total)						

**Demographic Characteristics (Safety Population)**

	<b>IC43 100 mcg (N=104) Median / Mean (range)</b>	<b>IC43 100 mcg w/o (N=98) Median / Mean (range)</b>	<b>IC43 200 mcg (N=101) Median / Mean (range)</b>	<b>Placebo (N=98) Median / Mean (range)</b>	<b>Total (N=401) Median / Mean (range)</b>
<b>Age (years)</b>	58.5 / 57.0 (20.0 - 82.0)	58.0 / 54.3 (18.0 - 78.0)	56.0 / 55.2 (18.0 - 79.0)	60.0 / 58.1 (20.0 - 80.0)	58.0 / 56.1 (18.0 - 82.0)
<b>Weight (kg)</b>	80.0 / 82.0 (40.0 - 140.0)	80.0 / 84.6 (50.0 - 159.0)	80.0 / 82.5 (40.0 - 145.0)	80.0 / 82.5 (42.0 - 180.0)	80.0 / 82.9 (40.0 - 180.0)
<b>Height (cm)</b>	170.0 / 170.8 (150.0 - 190.0)	175.0 / 173.5 (150.0 - 195.0)	170.0 / 171.5 (140.0 - 190.0)	170.0 / 171.5 (150.0 - 190.0)	172.0 / 171.8 (140.0 - 195.0)
<b>Sex</b>					
Male	64 (61.5)	70 (71.4)	72 (71.3)	61 (62.2)	267 (66.6)
Female	40 (38.5)	28 (28.6)	29 (28.7)	37 (37.8)	134 (33.4)

	<b>IC43 100 mcg (N=104) Median / Mean (range)</b>	<b>IC43 100 mcg w/o (N=98) Median / Mean (range)</b>	<b>IC43 200 mcg (N=101) Median / Mean (range)</b>	<b>Placebo (N=98) Median / Mean (range)</b>	<b>Total (N=401) Median / Mean (range)</b>
<b>Race</b>					
Caucasian	95 (91.3)	93 (94.9)	94 (93.1)	92 (93.9)	374 (93.3)
Asian	2 ( 1.9)	1 ( 1.0)	0 ( 0.0)	2 ( 2.0)	5 ( 1.2)
Black	1 ( 1.0)	0 ( 0.0)	2 ( 2.0)	1 ( 1.0)	4 ( 1.0)
Other	6 ( 5.8)	4 ( 4.1)	5 ( 5.0)	3 ( 3.1)	18 ( 4.5)

#### SOFA score at Visit 0 (Day 0) by group (Safety population)

	<b>IC43 100 mcg (N=104)</b>	<b>IC43 100 mcg w/o (N=98)</b>	<b>IC43 200 mcg (N=101)</b>	<b>Placebo (N=98)</b>	<b>Total (N=401)</b>
<b>SOFA score</b>					
Mean	8.6	7.8	8.0	8.7	8.3
SD	3.5	3.5	3.2	3.7	3.5
Median	8.0	8.0	8.0	9.0	8.0
Q1 / Q3	6.0 / 11.5	5.0 / 10.0	6.0 / 10.0	6.0 / 11.0	6.0 / 11.0

#### Primary Immunogenicity Analysis:

##### OprF/I specific IgG antibodies (ELISA) at Visit 2 (Day 14)

The primary immunogenicity analysis of OprF/I specific IgG antibodies on Visit 2 (Day 14) demonstrated significant differences between treatment groups ( $p < 0.0001$ ) with a significant pooled site effect ( $p = 0.0425$ ) in the ITT population. Pairwise comparisons revealed statistically significant differences ( $p < 0.0001$ ) between the placebo and each of the other groups (i.e. IC43 100 mcg and placebo, IC43 100 mcg w/o and placebo and IC43 200 mcg and placebo) and between IC43 100 mcg and IC43 200 mcg group ( $p = 0.0344$ ).

#### Primary & Secondary Objectives:

##### OprF/I specific IgG antibodies (ELISA) titers (GMT) at Day 0, 7, 14, 28, 42, 56, 70 and 90 by group (ITT population) – *primary objective: GMT at Day 14*

<b>Time point</b>	<b>OprF/I specific IgG antibodies [U/mL]</b>	<b>IC43 100 mcg (N=104)</b>	<b>IC43 100 mcg w/o (N=98)</b>	<b>IC43 200 mcg (N=101)</b>	<b>Placebo (N=98)</b>
<b>Day 0</b>	Geometric mean	120.6	113.2	112.5	108.5
	95% CI	[ 107.1, 135.9]	[ 102.4, 125.0]	[ 101.3, 124.9]	[ 99.9, 117.9]
	Total	104	98	101	98
<b>Day 7</b>	Geometric mean	161.6	171.1	186.0	111.5
	95% CI	[ 129.2, 202.1]	[ 133.9, 218.5]	[ 145.6, 237.6]	[ 100.7, 123.5]
	Total	95	87	92	82
<b>Day 14</b>	Geometric mean	1014.1	1902.2	2222.0	123.9
	95% CI	[ 655.0, 1569.9]	[ 1244.3, 2908.1]	[ 1380.5, 3576.5]	[ 107.7, 142.5]
	Total	80	72	72	71

Time point	OprF/l specific IgG antibodies [U/mL]	IC43 100 mcg (N=104)	IC43 100 mcg w/o (N=98)	IC43 200 mcg (N=101)	Placebo (N=98)
<b>Day 28</b>	Geometric mean	1528.2	2256.9	2399.6	149.7
	95% CI	[ 954.8,2445.8]	[1392.5,3658.0]	[1365.3,4217.2]	[ 108.7, 206.3]
	Total	54	47	41	33
<b>Day 42</b>	Geometric mean	1397.3	1259.8	2105.2	176.2
	95% CI	[ 836.7,2333.3]	[ 616.8,2573.1]	[ 959.8,4617.1]	[ 115.2, 269.3]
	Total	35	25	21	24
<b>Day 56</b>	Geometric mean	1223.5	1224.1	1732.6	146.7
	95% CI	[ 671.8,2228.3]	[ 591.3,2534.0]	[ 597.2,5026.8]	[ 101.3, 212.4]
	Total	20	20	13	18
<b>Day 70</b>	Geometric mean	1396.1	1549.6	855.5	147.4
	95% CI	[ 587.9,3315.3]	[ 246.7,9735.2]	[ 229.7,3186.2]	[ 92.9, 233.8]
	Total	8	6	11	13
<b>Day 90</b>	Geometric mean	586.4	645.9	1159.9	319.4
	95% CI	[ 279.3,1231.2]	[ 269.0,1550.4]	[ 456.1,2950.2]	[ 121.9, 836.8]
	Total	18	14	15	14

### Functional OprF/l-specific antibodies (OPA)

#### Changes in OPA titers from Day 0 to Day 14 by group (ITT population)

	IC43 100 mcg (N=104)	IC43 100 mcg w/o (N=98)	IC43 200 mcg (N=101)	Placebo (N=98)
<b>OPA titer ratio (Day 14/ Day 0)</b>				
Median (IQR (Interquartile Range))	2.1 (1.3 / 4.1)	2.6 (1.6 / 6.7)	3.4 (1.2 / 10.7)	1.1 (0.8 / 1.8)
<b>Increase from Day 0 to Day 14 <math>\geq</math> 2-fold</b>				
n (N)	44 ( 79)	48 ( 73)	46 ( 72)	14 ( 71)
% [95% CI]*	55.7% [44.7%, 66.1%]	65.8% [54.3%, 75.6%]	63.9% [52.4%, 74.0%]	19.7% [12.1%, 30.4%]

\*: 95% Confidence Intervals calculated according to Wilson's method recommended by Altman

A comparison of changes in OPA titer ratio from Day 0 to Day 14 for the four vaccination groups using a Kruskal-Wallis test demonstrated a statistically significant difference ( $p < 0.0001$ ) between treatment groups and between each IC43 group and placebo ( $p < 0.0001$ ), i.e. between IC43 100 mcg and placebo, between IC43 100 mcg w/o and placebo and between IC43 200 mcg and placebo.

**Invasive *P. aeruginosa* infection in ICU patients receiving IC43 vaccination versus placebo during hospital stay - at least one CEC (clinical endpoint committee)-confirmed *P. aeruginosa* infection by infectious event type and group (ITT population):**

	<b>IC43 100 mcg (N=104) No. (%) [95% CI]*</b>	<b>IC43 100 mcg w/o (N=98) No. (%) [95% CI]*</b>	<b>IC43 200 mcg (N=101) No. (%) [95% CI]*</b>	<b>Placebo (N=98) No. (%) [95% CI]*</b>	<b>p-value</b>
<b><i>P. aeruginosa</i> positive invasive disease</b>					
yes	14 (13.5) [8.2, 21.3]	11 (11.2) [6.4, 19.0]	14 (14.0) [8.5, 22.1]	6 ( 6.1) [2.8, 12.7]	0.2533
no	90 (86.5) [78.7, 91.8]	87 (88.8) [81.0, 93.6]	86 (86.0) [77.9, 91.5]	92 (93.9) [87.3, 97.2]	
Total	104	98	100	98	
not assessable	0	0	1	0	
<b><i>P. aeruginosa</i> positive infection overall</b>					
yes	22 (24.4) [16.7, 34.2]	24 (27.6) [19.3, 37.8]	27 (30.7) [22.0, 41.0]	22 (24.4) [16.7, 34.2]	0.7588
no	68 (75.6) [65.8, 83.3]	63 (72.4) [62.2, 80.7]	61 (69.3) [59.0, 78.0]	68 (75.6) [65.8, 83.3]	
Total	90	87	88	90	
not assessable	14	11	13	8	
<b><i>P. aeruginosa</i> positive Bacteremia</b>					
yes	10 (9.6) [5.3, 16.8]	7 (7.1) [3.5, 14.0]	9 (8.9) [4.8, 16.1]	6 (6.1) [2.8, 12.7]	0.7943
no	94 (90.4) [83.2, 94.7]	91 (92.9) [86.0, 96.5]	92 (91.1) [83.9, 95.2]	92 (93.9) [87.3, 97.2]	
Total	104	98	101	98	
not assessable	0	0	0	0	
<b><i>P. aeruginosa</i> positive Pneumonia</b>					
yes	5 (4.8) [2.1, 10.8]	4 (4.1) [1.6, 10.0]	6 (6.0) [2.8, 12.5]	0 (0.0) [0.0, 3.8]	0.0693
no	99 (95.2) [89.2, 97.9]	94 (95.9) [90.0, 98.4]	94 (94.0) [87.5, 97.2]	98 (100) [96.2, 100]	
Total	104	98	100	98	
not assessable	0	0	1	0	
<b><i>P. aeruginosa</i> positive Pneumonia (PN1 or PN2)</b>					
yes	1 (1.0) [0.2, 5.2]	1 (1.0) [0.2, 5.6]	4 (4.0) [1.6, 9.8]	0 (0.0) [0.0, 3.8]	0.1503
no	103 (99.0) [94.8, 99.8]	97 (99.0) [94.4, 99.8]	96 (96.0) [90.2, 98.4]	98 (100) [96.2, 100]	
Total	104	98	100	98	
not assessable	0	0	1	0	

<b><i>P. aeruginosa</i> positive Pneumonia (PN3, PN4 or PN5)</b>					
yes	4 (3.8) [1.5, 9.5]	3 (3.1) [1.0, 8.6]	2 (2.0) [0.6, 7.0]	0 (0.0) [0.0, 3.8]	0.2727
no	100 (96.2) [90.5, 98.5]	95 (96.9) [91.4, 99.0]	98 (98.0) [93.0, 99.4]	98 (100) [96.2, 100]	
Total	104	98	100	98	
not assessable	0	0	1	0	
<b><i>P. aeruginosa</i> positive Tracheobronchitis</b>					
yes	5 (4.8) [2.1, 10.8]	12 (12.2) [7.1, 20.2]	9 (9.0) [4.8, 16.2]	8 (8.2) [4.2, 15.3]	0.3022
no	99 (95.2) [89.2, 97.9]	86 (87.8) [79.8, 92.9]	91 (91.0) [83.8, 95.2]	90 (91.8) [84.7, 95.8]	
Total	104	98	100	98	
not assessable	0	0	1	0	
<b><i>P. aeruginosa</i> positive Tracheobronchitis (TB1 or TB2)</b>					
yes	0 (0.0) [0.0, 3.6]	6 (6.1) [2.8, 12.7]	2 (2.0) [0.6, 7.0]	4 (4.1) [1.6, 10.0]	0.0346
no	104 (100) [96.4, 100]	92 (93.9) [87.3, 97.2]	98 (98.0) [93.0, 99.4]	94 (95.9) [90.0, 98.4]	
Total	104	98	100	98	
not assessable	0	0	1	0	
<b><i>P. aeruginosa</i> positive Tracheobronchitis (TB3)</b>					
yes	5 (4.8) [2.1, 10.8]	6 (6.1) [2.8, 12.7]	7 (7.0) [3.4, 13.7]	4 (4.1) [1.6, 10.0]	0.8143
no	99 (95.2) [89.2, 97.9]	92 (93.9) [87.3, 97.2]	93 (93.0) [86.3, 96.6]	94 (95.9) [90.0, 98.4]	
Total	104	98	100	98	
not assessable	0	0	1	0	
<b><i>P. aeruginosa</i> positive Central venous catheter infection</b>					
yes	1 (1.2) [0.2, 6.4]	0 (0.0) [0.0, 4.9]	3 (4.1) [1.4, 11.4]	2 (2.6) [0.7, 9.1]	0.2863
no	83 (98.8) [93.6, 99.8]	74 (100) [95.1, 100]	70 (95.9) [88.6, 98.6]	74 (97.4) [90.9, 99.3]	
Total	84	74	73	76	
not assessable	20	24	28	22	
<b><i>P. aeruginosa</i> positive Wound infection</b>					
yes	9 (11.0) [5.9, 19.6]	6 (8.5) [3.9, 17.2]	8 (10.7) [5.5, 19.7]	6 (7.8) [3.6, 16.0]	0.8960
no	73 (89.0) [80.4, 94.1]	65 (91.5) [82.8, 96.1]	67 (89.3) [80.3, 94.5]	71 (92.2) [84.0, 96.4]	
Total	82	71	75	77	
not assessable	22	27	26	21	
<b><i>P. aeruginosa</i> positive Urinary tract infection</b>					
yes	4 (3.8) [1.5, 9.5]	5 (5.1) [2.2, 11.4]	7 (6.9) [3.4, 13.6]	9 (9.3) [5.0, 16.7]	0.4380
no	100 (96.2) [90.5, 98.5]	93 (94.9) [88.6, 97.8]	94 (93.1) [86.4, 96.6]	88 (90.7) [83.3, 95.0]	

Total	104	98	101	97	
not assessable	0	0	0	1	

**At least one P. aeruginosa positive culture by culture type and group (ITT population)**

Culture type	IC43 100 mcg (N=104) No. (%) [95% CI]*	IC43 100 mcg w/o (N=98) No. (%) [95% CI]*	IC43 200 mcg (N=101) No. (%) [95% CI]*	Placebo (N=98) No. (%) [95% CI]*	p-value
<b>Overall</b>					
Patients with at least one culture overall	39 (37.5) [28.8, 47.1]	37 (37.8) [28.8, 47.6]	40 (39.6) [30.6, 49.4]	32 (32.7) [24.2, 42.4]	0.7692
Total number of cultures overall	153	116	136	108	
<b>Bacterial blood culture</b>					
Patients with at least one bacterial blood culture	10 (9.6) [5.3, 16.8]	7 (7.1) [3.5, 14.0]	10 (9.9) [5.5, 17.3]	7 (7.1) [3.5, 14.0]	0.8322
Total number of bacterial blood cultures	17	15	20	15	
<b>Wound culture</b>					
Patients with at least one wound culture	9 (8.7) [4.6, 15.6]	6 (6.1) [2.8, 12.7]	9 (8.9) [4.8, 16.1]	6 (6.1) [2.8, 12.7]	0.7985
Total number of wound cultures	32	10	11	11	
<b>Urine culture</b>					
Patients with at least one urine culture	9 (8.7) [4.6, 15.6]	12 (12.2) [7.1, 20.2]	11 (10.9) [6.2, 18.5]	12 (12.2) [7.1, 20.2]	0.8202
Total number of urine cultures	21	21	19	18	
<b>Central venous catheter culture</b>					
Patients with at least one central venous catheter culture	2 (1.9) [0.5, 6.7]	0 (0.0) [0.0, 3.8]	4 (4.0) [1.6, 9.7]	5 (5.1) [2.2, 11.4]	0.0910
Total number of central	4	0	5	6	



<b>Culture type</b>	<b>IC43 100 mcg (N=104) No. (%) [95% CI]*</b>	<b>IC43 100 mcg w/o (N=98) No. (%) [95% CI]*</b>	<b>IC43 200 mcg (N=101) No. (%) [95% CI]*</b>	<b>Placebo (N=98) No. (%) [95% CI]*</b>	<b>p-value</b>
venous catheter cultures					
<b>Respiratory secretion culture</b>					
Patients with at least one respiratory secretion culture	33 (31.7) [23.6, 41.2]	27 (27.6) [19.7, 37.1]	31 (30.7) [22.5, 40.3]	21 (21.4) [14.5, 30.5]	0.3515
Total number of respiratory secretion cultures	79	70	81	58	

### Survival/ Mortality

The percentage of patients alive at the end of the study was 64.4% (n=67) in the IC43 100 mcg group, 71.4% (n=70) in the IC43 100 mcg w/o group, 62.4% (n=63) in the IC43 200 mcg group and 57.1% (n=56) in the placebo group.

The percentage of patients alive at Day 28 was 73.2% (n=71) in the IC43 100 mcg group, 78.3% (n=72) in the IC43 100 mcg w/o group, 74.0% (n=71) in the IC43 200 mcg group and 60.0% (n=54) in the placebo group.

The overall mortality rate and day 28-mortality rate were higher in the placebo group compared to the IC43 groups (42.9% (placebo) versus 35.6% (IC43 100 mcg), 28.6% (IC43 100 mcg w/o), 37.6% (IC43 200 mcg) for overall mortality; 40% (placebo) versus 26.8% (IC43 100 mcg), 21.7% (IC43 100 mcg w/o), 26.0% (IC43 200 mcg) for day 28-mortality). The difference to placebo in mortality was significant for the IC43 100 mcg w/o group for overall survival (p=0.0202) and for day 28 survival (p=0.0099). It appears that patients alive at study end had a higher OprF/I specific IgG titer at day 14 compared to those who died after day 14. A cox regression analysis demonstrated a significant prognostic value of the OprF/I IgG titer at Visit 2 (Day 14) on survival, independent of a non-significant group effect in the ITT population at Day 14.

Larger, sufficiently powered Phase III studies would be required to validate and verify any vaccine effect on *P. aeruginosa* infection and mortality.

### Length of Stay in ICU/ hospital

The mean length of stay in ICU was 26.6 days in the IC43 100 mcg group, 24.3 days in the IC43 100 mcg w/o group, 24.0 days in the IC43 200 mcg group and 23.5 days in the placebo group (non-censored patients only, Safety population).

The mean length of stay in hospital (excluding ICU stay) was 15.2 days in the IC43 100 mcg group, 13.9 days in the IC43 100 mcg w/o group, 14.4 days in the IC43 200 mcg group and 12.4 days in the placebo group (non-censored patients only, Safety population).

**SOFA score**

The mean SOFA scores for patients alive at the end of the study were 8.24 in the IC43 100 mcg group, 8.00 in the IC43 100 mcg w/o group, 7.37 in the IC43 200 mcg group and 8.39 in the placebo group. The mean SOFA scores for patients dead at the end of the study were 9.38 in the IC43 100 mcg group, 7.36 in the IC43 100 mcg w/o group, 8.97 in the IC43 200 mcg group and 9.02 in the placebo group.

**Concomitant antibiotics**

Number of antibiotic free days since first vaccination (ITT population)

	<b>IC43 100 mcg (N=104) No. (%)</b>	<b>IC43 100 mcg w/o (N=98) No. (%)</b>	<b>IC43 200 mcg (N=101) No. (%)</b>	<b>Placebo (N=98) No. (%)</b>
<b>Number of antibiotic-free days since first vaccination</b>				
Mean	38.9	39.6	38.0	35.1
SD	36.8	33.2	35.0	35.0
Median	38.5	41.0	27.0	24.5
Q1 / Q3	3.0 / 66.0	5.0 / 74.0	1.0 / 73.0	2.0 / 66.0
Min / Max	0.0 / 214.0	0.0 / 101.0	0.0 / 95.0	0.0 / 144.0

The number of antibiotic free days since first vaccination was very similar in all treatment groups.

**Systemic Tolerability:**

At screening (Day 0), abnormalities in vital signs (pulse, blood pressure) within 1 hour of vaccination were reported in one patient in the IC43 100 mcg group ( "Shock" within 1 hour after vaccination) and in one patient in the IC43 100 mcg w/o group ( "Increased blood pressure" within 1 hour after vaccination). No abnormalities were reported at Visit 1 (Day 7).

At screening (Day 0), new abnormalities or any worsening in intensity or frequency of a pre-existing condition during or within 1 hour after the vaccination were reported by one patient in the placebo group ( "Haemorrhage intracranial" within 1 hour after vaccination). At Visit 1 (Day 7), abnormalities were reported by one patient in the IC43 100 mcg w/o group ( "Septic shock" already present at vaccination time)

**Local Tolerability: Presence and Severity for each local tolerability symptom by time-point and group (Safety population)**

<b>Time-point</b>	<b>IC43 100 mcg (N=104) No. (%) [95% CI]*</b>	<b>IC43 100 mcg w/o (N=98) No. (%) [95% CI]*</b>	<b>IC43 200 mcg (N=101) No. (%) [95% CI]*</b>	<b>Placebo (N=98) No. (%) [95% CI]*</b>
<b>Erythema/Redness</b>				
Screening Visit (Visit 0), 1h after IMP administration	2 (100) [34.2, 100]	0 (0.0)	2 (100) [34.2, 100]	0 (0.0)
Visit 1, before IMP administration	1 (100) [20.7, 100]	0 (0.0)	0 (0.0)	0 (0.0)
Visit 1, 1h after IMP administration	2 (100) [34.2, 100]	0 (0.0)	2 (100) [34.2, 100]	2 (100) [34.2, 100]

Visit 2	1 (100) [20.7, 100]	0 (0.0)	0 (0.0)	0 (0.0)
<b>Induration</b>				
Screening Visit (Visit 0), 1h after IMP administration	1 (100) [20.7, 100]	0 (0.0)	0 (0.0)	0 (0.0)
Visit 1, before IMP administration	2 (100) [34.2, 100]	0 (0.0)	1 (100) [20.7, 100]	0 (0.0)
Visit 1, 1h after IMP administration	1 (100) [20.7, 100]	0 (0.0)	0 (0.0)	0 (0.0)
Visit 2	1 (100) [20.7, 100]	0 (0.0)	0 (0.0)	0 (0.0)
Discharge visit A	0 (0.0)	0 (0.0)	1 (100) [20.7, 100]	0 (0.0)
<b>Pain</b>				
Visit 1, before IMP administration	1 (100) [20.7, 100]	0 (0.0)	0 (0.0)	0 (0.0)
Visit 1, 1h after IMP administration	1 (100) [20.7, 100]	0 (0.0)	1 (100) [20.7, 100]	2 (100) [34.2, 100]
<b>Swelling</b>				
Screening Visit (Visit 0), 1h after IMP administration	0 (0.0)	0 (0.0)	0 (0.0)	1 (100) [20.7, 100]
Visit 1, before IMP administration	0 (0.0)	0 (0.0)	0 (0.0)	1 (100) [20.7, 100]
Visit 1, 1h after IMP administration	1 (100) [20.7, 100]	0 (0.0)	1 (100) [20.7, 100]	1 (100) [20.7, 100]

No episodes of itching or tenderness were recorded.

All local tolerability symptoms were either < grade 1 or mild (grade 1).

**Safety Overview:**

<b>Patients with at least one/Total number of</b>	<b>IC43 100 mcg (N=104) No. (%) [95% CI]*</b>	<b>IC43 100 mcg w/o (N=98) No. (%) [95% CI]*</b>	<b>IC43 200 mcg (N=101) No. (%) [95% CI]*</b>	<b>Placebo (N=98) No. (%) [95% CI]*</b>	<b>Total (N=401) No. (%)</b>
<b>AE</b>	95 (91.3) [84.4, 95.4]	83 (84.7) [76.3, 90.5]	87 (86.1) [78.1, 91.6]	87 (88.8) [81.0, 93.6]	352 (87.8)
AEs	648	454	480	495	2077
<b>related AE</b>	11 (10.6) [6.0, 18.0]	3 (3.1) [1.0, 8.6]	10 (9.9) [5.5, 17.3]	6 (6.1) [2.8, 12.7]	30 (7.5)
related AEs	15	3	13	8	39
<b>unrelated AE</b>	94 (90.4) [83.2, 94.7]	82 (83.7) [75.1, 89.7]	87 (86.1) [78.1, 91.6]	87 (88.8) [81.0, 93.6]	350 (87.3)
unrelated AEs	633	451	467	487	2038
<b>medically attended AE</b>	90 (86.5) [78.7, 91.8]	78 (79.6) [70.6, 86.4]	82 (81.2) [72.5, 87.6]	85 (86.7) [78.6, 92.1]	335 (83.5)
medically attended AEs	474	382	372	389	1617

<b>Patients with at least one/Total number of</b>	<b>IC43 100 mcg (N=104) No. (%) [95% CI]*</b>	<b>IC43 100 mcg w/o (N=98) No. (%) [95% CI]*</b>	<b>IC43 200 mcg (N=101) No. (%) [95% CI]*</b>	<b>Placebo (N=98) No. (%) [95% CI]*</b>	<b>Total (N=401) No. (%)</b>
<b>severe AE</b>	55 (52.9) [43.4, 62.2]	43 (43.9) [34.5, 53.7]	54 (53.5) [43.8, 62.9]	53 (54.1) [44.2, 63.6]	205 (51.1)
severe AEs	96	64	90	104	354
<b>related severe AE</b>	2 (1.9) [0.5, 6.7]	0 (0.0) [0.0, 3.8]	0 (0.0) [0.0, 3.7]	0 (0.0) [0.0, 3.8]	2 (0.5)
related severe AEs	2	0	0	0	2
<b>unrelated severe AE</b>	54 (51.9) [42.4, 61.3]	43 (43.9) [34.5, 53.7]	54 (53.5) [43.8, 62.9]	53 (54.1) [44.2, 63.6]	204 (50.9)
unrelated severe AEs	94	64	90	104	352
<b>AE without action on IMP</b>	95 (91.3) [84.4, 95.4]	83 (84.7) [76.3, 90.5]	87 (86.1) [78.1, 91.6]	87 (88.8) [81.0, 93.6]	352 (87.8)
AEs without action on IMP	647	454	480	495	2076
<b>AE with action on IMP</b>	1 (1.0) [0.2, 5.2]	0 (0.0) [0.0, 3.8]	0 (0.0) [0.0, 3.7]	0 (0.0) [0.0, 3.8]	1 (0.2)
AEs with action on IMP	1	0	0	0	1
<b>serious AE</b>	59 (56.7) [47.1, 65.8]	38 (38.8) [29.7, 48.7]	52 (51.5) [41.9, 61.0]	53 (54.1) [44.2, 63.6]	202 (50.4)
serious AEs	87	48	70	81	286
<b>related serious AE</b>	2 (1.9) [0.5, 6.7]	0 (0.0) [0.0, 3.8]	0 (0.0) [0.0, 3.7]	0 (0.0) [0.0, 3.8]	2 (0.5)
related serious AEs	2	0	0	0	2
<b>unrelated serious AE</b>	58 (55.8) [46.2, 64.9]	38 (38.8) [29.7, 48.7]	52 (51.5) [41.9, 61.0]	53 (54.1) [44.2, 63.6]	201 (50.1)
unrelated serious AEs	85	48	70	81	284

### Frequency of Common Adverse Events and Common Adverse Events by System Organ Class and Preferred Term (Safety Population)

includes SOC's only where at least one AE of this SOC was observed and details of preferred term only where a statistically significant difference between treatment groups has been demonstrated

<b>System organ class Preferred term</b>	<b>IC43 100 mcg (N=104) No. (%) [95% CI]*</b>	<b>IC43 100 mcg w/o (N=98) No. (%) [95% CI]*</b>	<b>IC43 200 mcg (N=101) No. (%) [95% CI]*</b>	<b>Placebo (N=98) No. (%) [95% CI]*</b>	<b>p-value</b>
<b>Infections and infestations</b>	69 (66.3) [56.8, 74.7]	63 (64.3) [54.4, 73.1]	62 (61.4) [51.6, 70.3]	64 (65.3) [55.5, 74.0]	0.8995
Catheter sepsis	0 (0.0) [0.0, 3.6]	0 (0.0) [0.0, 3.8]	0 (0.0) [0.0, 3.7]	3 (3.1) [1.0, 8.6]	0.0285

<b>System organ class</b> Preferred term	<b>IC43 100 mcg (N=104) No. (%) [95% CI]*</b>	<b>IC43 100 mcg w/o (N=98) No. (%) [95% CI]*</b>	<b>IC43 200 mcg (N=101) No. (%) [95% CI]*</b>	<b>Placebo (N=98) No. (%) [95% CI]*</b>	<b>p-value</b>
<b>Respiratory, thoracic and mediastinal disorders</b>	33 (31.7) [23.6, 41.2]	27 (27.6) [19.7, 37.1]	28 (27.7) [19.9, 37.1]	28 (28.6) [20.6, 38.2]	0.9106
<b>Gastrointestinal disorders</b>	27 (26.0) [18.5, 35.1]	16 (16.3) [10.3, 24.9]	26 (25.7) [18.2, 35.0]	26 (26.5) [18.8, 36.0]	0.2540
<b>Cardiac disorders</b>	31 (29.8) 21.9, 39.2]	18 (18.4) [11.9, 27.2]	19 (18.8) [12.4, 27.5]	25 (25.5) [17.9, 35.0]	0.1632
<b>General disorders and administration site conditions</b>	28 (26.9) [19.3, 36.2]	15 (15.3) [9.5, 23.7]	17 (16.8) [10.8, 25.3]	19 (19.4) [12.8, 28.3]	0.1787
Generalised oedema	6 (5.8) [2.7, 12.0]	0 (0.0) [0.0, 3.8]	0 (0.0) [0.0, 3.7]	2 (2.0) [0.6, 7.1]	0.0056
<b>Blood and lymphatic system disorders</b>	21 (20.2) [13.6,28.9]	17 (17.3) [11.1,26.0]	20 (19.8) [13.2,28.6]	15 (15.3) [9.5,23.7]	0.7876
<b>Renal and urinary disorders</b>	20 (19.2) [12.8, 27.8]	12 (12.2) [7.1, 20.2]	20 (19.8) [13.2, 28.6]	18 (18.4) [11.9, 27.2]	0.4551
<b>Vascular disorders</b>	24 (23.1) [16.0, 32.0]	13 (13.3) [7.9, 21.4]	12 (11.9) [6.9, 19.6]	18 (18.4) [11.9, 27.2]	0.1332
<b>Nervous system disorders</b>	15 (14.4) [8.9, 22.4]	16 (16.3) [10.3, 24.9]	14 (13.9) [8.4, 21.9]	20 (20.4) [13.6, 29.4]	0.6032
<b>Metabolism and nutrition disorders</b>	17 (16.3) [10.5, 24.6]	10 (10.2) [5.6, 17.8]	15 (14.9) [9.2, 23.1]	18 (18.4) [11.9, 27.2]	0.4147
Diabetes mellitus	0 (0.0) [0.0, 3.6]	0 (0.0) [0.0, 3.8]	3 (3.0) [1.0, 8.4]	0 (0.0) [0.0, 3.8]	0.0441
<b>Investigations</b>	18 (17.3) [11.2, 25.7]	9 (9.2) [4.9, 16.5]	15 (14.9) [9.2, 23.1]	15 (15.3) [9.5, 23.7]	0.3736
<b>Skin and subcutaneous tissue disorders</b>	19 (18.3) [12.0, 26.8]	6 (6.1) [2.8, 12.7]	15 (14.9) [9.2, 23.1]	10 (10.2) [5.6, 17.8]	0.0465
<b>Psychiatric disorders</b>	13 (12.5) [7.5, 20.2]	11 (11.2) [6.4, 19.0]	8 (7.9) [4.1, 14.9]	14 (14.3) [8.7, 22.6]	0.5347
Anxiety	5 (4.8) [2.1, 10.8]	0 (0.0) [0.0, 3.8]	0 (0.0) [0.0, 3.7]	1 (1.0) [0.2, 5.6]	0.0158
<b>Injury, poisoning and procedural complications</b>	10 (9.6) [5.3, 16.8]	7 (7.1) [3.5, 14.0]	10 (9.9) [5.5, 17.3]	9 (9.2) [4.9, 16.5]	0.9143
<b>Hepatobiliary disorders</b>	10 (9.6) [5.3, 16.8]	4 (4.1) [1.6, 10.0]	6 (5.9) [2.8, 12.4]	9 (9.2) [4.9, 16.5]	0.3606
<b>Eye disorders</b>	4 (3.8) [1.5, 9.5]	5 (5.1) [2.2, 11.4]	4 (4.0) [1.6, 9.7]	3 (3.1) [1.0, 8.6]	0.9203

<b>System organ class</b> Preferred term	<b>IC43 100 mcg (N=104)</b> No. (%) [95% CI]*	<b>IC43 100 mcg w/o (N=98)</b> No. (%) [95% CI]*	<b>IC43 200 mcg (N=101)</b> No. (%) [95% CI]*	<b>Placebo (N=98)</b> No. (%) [95% CI]*	<b>p-value</b>
<b>Musculoskeletal and connective tissue disorders</b>	7 (6.7) [3.3, 13.2]	4 (4.1) [1.6, 10.0]	3 (3.0) [1.0, 8.4]	2 (2.0) [0.6, 7.1]	0.3835
<b>Endocrine disorders</b>	1 (1.0) [0.2, 5.2]	0 (0.0) [0.0, 3.8]	2 (2.0) [0.5, 6.9]	4 (4.1) [1.6, 10.0]	0.1316
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	2 (1.9) [0.5, 6.7]	0 (0.0) [0.0, 3.8]	1 (1.0) [0.2, 5.4]	1 (1.0) [0.2, 5.6]	0.9049
<b>Surgical and medical procedures</b>	0 (0.0) [0.0, 3.6]	1 (1.0) [0.2, 5.6]	3 (3.0) [1.0, 8.4]	0 (0.0) [0.0, 3.8]	0.1326
<b>Congenital, familial and genetic disorders</b>	1 (1.0) [0.2, 5.2]	1 (1.0) [0.2, 5.6]	1 (1.0) [0.2, 5.4]	0 (0.0) [0.0, 3.8]	1.0000
<b>Reproductive system and breast disorders</b>	0 (0.0) [0.0, 3.6]	1 (1.0) [0.2, 5.6]	1 (1.0) [0.2, 5.4]	1 (1.0) [0.2, 5.6]	0.7133
<b>Ear and labyrinth disorders</b>	1 (1.0) [0.2, 5.2]	0 (0.0) [0.0, 3.8]	0 (0.0) [0.0, 3.7]	1 (1.0) [0.2, 5.6]	0.8690
<b>Immune system disorders</b>	0 (0.0) [0.0, 3.6]	1 (1.0) [0.2, 5.6]	0 (0.0) [0.0, 3.7]	0 (0.0) [0.0, 3.8]	0.4888

Patients are counted only once per System organ class or Preferred term, percentages are based on N

\*: Two-sided 95% confidence intervals calculated according Altman

#### Frequency of Serious Adverse Events and Common Adverse Events by System Organ Class and Preferred Term (Safety Population)

<b>System organ class</b>	<b>Preferred term</b>	<b>IC43 100 mcg (N=104)</b> No. (%) [95% CI]*	<b>IC43 100 mcg w/o (N=98)</b> No. (%) [95% CI]*	<b>IC43 200 mcg (N=101)</b> No. (%) [95% CI]*	<b>Placebo (N=98)</b> No. (%) [95% CI]*	<b>p-value**</b>
<b>Cardiac disorders</b>		21 (20.2) [13.6,28.9]	12 (12.2) [ 7.1,20.2]	14 (13.9) [ 8.4,21.9]	16 (16.3) [10.3,24.9]	0.4402
	Cardiac arrest	10 ( 9.6) [ 5.3,16.8]	4 ( 4.1) 1.6,10.0]	8 ( 7.9) [ 4.1,14.9]	10 (10.2) [ 5.6,17.8]	0.3575
	Cardiac failure	2 ( 1.9) [ 0.5, 6.7]	6 ( 6.1) [ 2.8,12.7]	1 ( 1.0) [ 0.2, 5.4]	3 ( 3.1) [ 1.0, 8.6]	0.1913

System organ class	Preferred term	IC43 100 mcg (N=104) No. (%) [95% CI]*	IC43 100 mcg w/o (N=98) No. (%) [95% CI]*	IC43 200 mcg (N=101) No. (%) [95% CI]*	Placebo (N=98) No. (%) [95% CI]*	p-value**
	Cardio-respiratory arrest	2 ( 1.9) [ 0.5, 6.7]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	1 ( 1.0) 0.2, 5.6]	0.9049
	Arrhythmia	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	1 ( 1.0) [ 0.2, 5.6]	1.0000
	Left ventricular failure	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	2 ( 2.0) [ 0.5, 6.9]	0 ( 0.0) [ 0.0, 3.8]	0.5717
	Cardiac failure acute	1 ( 1.0) [ 0.2, 5.2]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.8690
	Ventricular fibrillation	2 ( 1.9) [ 0.5, 6.7]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.2483
	Acute myocardial infarction	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Atrioventricular block complete	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Bradycardia	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Cardiogenic shock	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Cardiopulmonary failure	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.4888
<b>Infections and infestations</b>		16 (15.4) [ 9.7,23.5]	9 ( 9.2) [ 4.9,16.5]	19 (18.8) [12.4,27.5]	14 (14.3) [ 8.7,22.6]	0.2707
	Septic shock	7 ( 6.7) [ 3.3,13.2]	6 ( 6.1) [ 2.8,12.7]	10 ( 9.9) [ 5.5,17.3]	10 (10.2) [ 5.6,17.8]	0.6312
	Pneumonia	4 ( 3.8) [ 1.5, 9.5]	1 ( 1.0) [ 0.2, 5.6]	4 ( 4.0) [ 1.6, 9.7]	2 ( 2.0) [ 0.6, 7.1]	0.5498
	Sepsis	2 ( 1.9) [ 0.5, 6.7]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	2 ( 2.0) [ 0.6, 7.1]	0.6995
	Bacteraemia	1 ( 1.0) [ 0.2, 5.2]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.8690
	Meningitis	1 ( 1.0) [ 0.2, 5.2]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.8690
	Abdominal abscess	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Abdominal infection	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406

System organ class	Preferred term	IC43 100 mcg (N=104) No. (%) [95% CI]*	IC43 100 mcg w/o (N=98) No. (%) [95% CI]*	IC43 200 mcg (N=101) No. (%) [95% CI]*	Placebo (N=98) No. (%) [95% CI]*	p-value**
	Abscess limb	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Bronchopneumonia	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Cellulitis	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Colostomy infection	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Endocarditis bacterial	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Enterococcal sepsis	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Extradural abscess	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.4888
	Fungaemia	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Meningitis bacterial	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Tracheostomy infection	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.4888
	Urinary tract infection	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
<b>Respiratory, thoracic and mediastinal disorders</b>	Wound infection	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
		11 (10.6) [ 6.0,18.0]	12 (12.2) [ 7.1,20.2]	10 ( 9.9) [ 5.5,17.3]	9 ( 9.2) [ 4.9,16.5]	0.9120
	Respiratory failure	3 ( 2.9) [ 1.0, 8.1]	5 ( 5.1) [ 2.2,11.4]	2 ( 2.0) [ 0.5, 6.9]	5 ( 5.1) [ 2.2,11.4]	0.5503
	Acute respiratory distress syndrome	2 ( 1.9) [ 0.5, 6.7]	1 ( 1.0) [ 0.2, 5.6]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.9049
	Hypoxia	3 ( 2.9) [ 1.0, 8.1]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.1826
	Acute respiratory failure	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.6149



<b>System organ class</b>	<b>Preferred term</b>	<b>IC43 100 mcg (N=104) No. (%) [95% CI]*</b>	<b>IC43 100 mcg w/o (N=98) No. (%) [95% CI]*</b>	<b>IC43 200 mcg (N=101) No. (%) [95% CI]*</b>	<b>Placebo (N=98) No. (%) [95% CI]*</b>	<b>p-value**</b>
	Chronic obstructive pulmonary disease	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Pneumonia aspiration	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.6149
	Pneumothorax	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	1 ( 1.0) [ 0.2, 5.6]	0.6149
	Pulmonary haemorrhage	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.8690
	Respiratory arrest	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	2 ( 2.0) [ 0.6, 7.1]	0.1185
	Bronchospasm	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.4888
	Dyspnoea	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Haemothorax	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.4888
	Respiratory disorder	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Respiratory distress	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Respiratory tract haemorrhage	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Thoracic haemorrhage	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
<b>Nervous system disorders</b>	Tracheal stenosis	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.4888
		5 ( 4.8) [ 2.1,10.8]	4 ( 4.1) [ 1.6,10.0]	4 ( 4.0) [ 1.6, 9.7]	9 ( 9.2) [ 4.9,16.5]	0.3876
	Brain oedema	1 ( 1.0) [ 0.2, 5.2]	1 ( 1.0) [ 0.2, 5.6]	1 ( 1.0) [ 0.2, 5.4]	2 ( 2.0) [ 0.6, 7.1]	0.8785
	Ischaemic stroke	1 ( 1.0) [ 0.2, 5.2]	2 ( 2.0) [ 0.6, 7.1]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.6596
	Cerebrovascular accident	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	2 ( 2.0) [ 0.6, 7.1]	0.2386

System organ class	Preferred term	IC43 100 mcg (N=104) No. (%) [95% CI]*	IC43 100 mcg w/o (N=98) No. (%) [95% CI]*	IC43 200 mcg (N=101) No. (%) [95% CI]*	Placebo (N=98) No. (%) [95% CI]*	p-value**
	Intracranial pressure increased	1 ( 1.0) [ 0.2, 5.2]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.8690
	Neurological decompensation	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.8690
	Anoxic encephalopathy	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Cerebral artery occlusion	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.4888
	Cerebral haemorrhage	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Cerebral infarction	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Critical illness polyneuropathy	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Grand mal convulsion	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Haemorrhage intracranial	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Hemiparesis	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Hydrocephalus	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Subarachnoid haemorrhage	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Vocal cord paralysis	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
General disorders and administration site conditions		7 ( 6.7) [ 3.3,13.2]	2 ( 2.0) [ 0.6, 7.1]	3 ( 3.0) [ 1.0, 8.4]	7 ( 7.1) [ 3.5,14.0]	0.2218
	Multi-organ failure	4 ( 3.8) [ 1.5, 9.5]	1 ( 1.0) [ 0.2, 5.6]	2 ( 2.0) [ 0.5, 6.9]	6 ( 6.1) [ 2.8,12.7]	0.1962
	Brain death	1 ( 1.0) [ 0.2, 5.2]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.8690

System organ class	Preferred term	IC43 100 mcg (N=104) No. (%) [95% CI]*	IC43 100 mcg w/o (N=98) No. (%) [95% CI]*	IC43 200 mcg (N=101) No. (%) [95% CI]*	Placebo (N=98) No. (%) [95% CI]*	p-value**
	Death	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Pyrexia	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
Vascular disorders	Sudden death	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Systemic inflammatory response syndrome	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
		6 ( 5.8) [ 2.7,12.0]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	5 ( 5.1) [ 2.2,11.4]	0.0202
	Hypotension	2 ( 1.9) [ 0.5, 6.7]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.5225
	Shock	2 ( 1.9) [ 0.5, 6.7]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.5225
	Deep vein thrombosis	2 ( 1.9) [ 0.5, 6.7]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.2483
	Shock haemorrhagic	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	2 ( 2.0) [ 0.6, 7.1]	0.1185
	Arterial thrombosis limb	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
Gastrointestinal disorders	Extremity necrosis	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
		4 ( 3.8) [ 1.5, 9.5]	1 ( 1.0) [ 0.2, 5.6]	4 ( 4.0) [ 1.6, 9.7]	2 ( 2.0) [ 0.6, 7.1]	0.5498
	Intra-abdominal haemorrhage	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	1 ( 1.0) [ 0.2, 5.4]	1 ( 1.0) [ 0.2, 5.6]	0.7133
	Acute abdomen	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Gastric haemorrhage	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Ileal perforation	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Ileus	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888

System organ class	Preferred term	IC43 100 mcg (N=104) No. (%) [95% CI]*	IC43 100 mcg w/o (N=98) No. (%) [95% CI]*	IC43 200 mcg (N=101) No. (%) [95% CI]*	Placebo (N=98) No. (%) [95% CI]*	p-value**
	Intestinal fistula	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Lower gastrointestinal haemorrhage	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Mechanical ileus	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Peritoneal necrosis	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Rectal haemorrhage	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
<b>Renal and urinary disorders</b>		0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	3 ( 3.0) [ 1.0, 8.4]	4 ( 4.1) [ 1.6, 10.0]	0.1128
	Renal failure	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	2 ( 2.0) [ 0.5, 6.9]	2 ( 2.0) [ 0.6, 7.1]	0.2664
	Renal failure acute	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	2 ( 2.0) [ 0.6, 7.1]	0.1486
<b>Injury, poisoning and procedural complications</b>	Anuria	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
		1 ( 1.0) [ 0.2, 5.2]	1 ( 1.0) [ 0.2, 5.6]	2 ( 2.0) [ 0.5, 6.9]	1 ( 1.0) [ 0.2, 5.6]	0.9383
	Brain herniation	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.4888
	Gastrointestinal stoma complication	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Hepatic haematoma	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Implant tissue necrosis	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
<b>Metabolism and nutrition disorders</b>	Tracheal haemorrhage	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
		2 ( 1.9) [ 0.5, 6.7]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.7081

System organ class	Preferred term	IC43 100 mcg (N=104) No. (%) [95% CI]*	IC43 100 mcg w/o (N=98) No. (%) [95% CI]*	IC43 200 mcg (N=101) No. (%) [95% CI]*	Placebo (N=98) No. (%) [95% CI]*	p-value**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hypoglycaemia	2 ( 1.9) [ 0.5, 6.7]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.7081
		2 ( 1.9) [ 0.5, 6.7]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	1 ( 1.0) [ 0.2, 5.6]	0.9049
	Glioblastoma	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Hodgkin's disease	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Metastatic neoplasm	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Neoplasm progression	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
Hepatobiliary disorders		1 ( 1.0) [ 0.2, 5.2]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.8070
	Cholangitis	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Cholecystitis acute	0 ( 0.0) [ 0.0, 3.6]	1 ( 1.0) [ 0.2, 5.6]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.4888
	Hepatic failure	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
Investigations		2 ( 1.9) [ 0.5, 6.7]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	0.2483
	Ammonia increased	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Oxygen consumption increased	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
Blood and lymphatic system disorders		0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888
	Thrombocytopenia	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	1 ( 1.0) [ 0.2, 5.6]	0.4888

<b>System organ class</b>	<b>Preferred term</b>	<b>IC43 100 mcg (N=104) No. (%) [95% CI]*</b>	<b>IC43 100 mcg w/o (N=98) No. (%) [95% CI]*</b>	<b>IC43 200 mcg (N=101) No. (%) [95% CI]*</b>	<b>Placebo (N=98) No. (%) [95% CI]*</b>	<b>p- value**</b>
<b>Musculoskeletal and connective tissue disorders</b>		1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
	Myalgia	1 ( 1.0) [ 0.2, 5.2]	0 ( 0.0) [ 0.0, 3.8]	0 ( 0.0) [ 0.0, 3.7]	0 ( 0.0) [ 0.0, 3.8]	1.0000
<b>Skin and subcutaneous tissue disorders</b>		0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406
	Drug rash with eosinophilia and systemic symptoms	0 ( 0.0) [ 0.0, 3.6]	0 ( 0.0) [ 0.0, 3.8]	1 ( 1.0) [ 0.2, 5.4]	0 ( 0.0) [ 0.0, 3.8]	0.7406

Subjects are counted only once per System organ class or Preferred term, percentages are based on N

\*: Two-sided 95% confidence intervals calculated according Altman

\*\*: Fisher-Freeman-Halton Test