Clinical trial results:
A Phase II randomized, placebo-controlled, double-blind, dose ranging study of a Clostridium difficile toxoid vaccine (ACAM-CDIFF) in subjects with Clostridium difficile-associated infection(CDI)

Summary

EudraCT number	2008-004907-69
Trial protocol	GB
Global end of trial date	11 July 2011

Results information

Result version number	v1 (current)
This version publication date	16 February 2016
First version publication date	22 July 2015

Trial information

Trial identification

Sponsor protocol code	H-030-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00772343
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur Inc
Sponsor organisation address	1 Discovery Drive, Swiftwater, United States, 18370
Public contact	Director, Clinical Development, Sanofi Pasteur Inc, 1 570-957-0746, guy.debruyn@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur Inc, 1 570-957-0746, guy.debruyn@sanofipasteur.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	05 December 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 July 2011
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the event rate of CDI in groups assigned to ACAM-CDIFF vaccine (pooled groups) versus placebo in the 9 week period after the third dose of study vaccine (Study Days 29 to 91) in subjects with primary CDI up to 12 days prior to the first dose of study vaccine, receiving antibiotic standard of care. Primary CDI is defined as a documented, laboratory-confirmed CDI event that is either the first in the subject's history or is occurring more than 90 days after a prior event.
This study was halted due to operational futility before the planned number of subjects was enrolled. The actual number of subjects enrolled (116) was far below what was originally planned (612). A formal analysis of event rates could not be performed and the analyses are displayed descriptively.
The summary and analysis were performed on the per-protocol analysis set and the intent-to-treat analysis set.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

During the screening period, subjects were to be treated according to recommended clinical guidelines, which could include metronidazole or vancomycin.

Evidence for comparator:

Not applicable

Actual start date of recruitment	11 May 2009
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	United Kingdom: 39
Country: Number of subjects enrolled	United States: 77
Worldwide total number of subjects	116
EEA total number of subjects	39

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)	64
From 65 to 84 years	40
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 11 May 2009 to 18 November 2010 at 11 clinical centers in the United Kingdom and from 22 December 2009 to 11 July 2011 at 26 clinical centers in the United States.

Pre-assignment

Screening details:

A total of 116 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled; 113 subjects were vaccinated.

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, Assessor

Blinding implementation details:

All subjects and all study site personnel, with the exception of the pharmacist(s) (or designee) who prepared the study vaccine for administration, were blinded to the treatment schedule. The pharmacist (or designee) was not to inform any of the investigational staff of the treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	50 µg + AlOH

Arm description:

Subjects who received 3 injections of 50 µg ACAM-CDIFF vaccine plus aluminum hydroxide (AlOH) adjuvant administered on Days 0, 7, and 28.

Arm type	Experimental
Investigational medicinal product name	ACAM-CDIFF™ Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, intramuscular, 3 injections administered on Days 0, 7, and 28.

Arm title	100 µg

Arm description:

Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine (no adjuvant) administered on Days 0, 7, and 28.

Arm type	Experimental
Investigational medicinal product name	ACAM-CDIFF™ Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, intramuscular, 3 injections administered on Days 0, 7, and 28.

Arm title	100 µg + AlOH

Arm description:

Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine plus AlOH adjuvant administered on Days 0, 7, and 28.

Arm type	Experimental
Investigational medicinal product name	ACAM-CDIFF™ Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, intramuscular, 3 injections administered on Days 0, 7, and 28.

Arm title	Placebo

Arm description:

Subjects who received 3 injections of placebo vaccine (0.9% normal saline) administered on Days 0, 7, and 28.

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

Dosage and administration details:

0.5 mL dose, intramuscular, 3 injections administered on Days 0, 7, and 28.

Number of subjects in period 1[1]	50 µg + AlOH	100 µg	100 µg + AlOH
Started	17	18	40
Completed	11	16	35
Not completed	6	2	5
Consent withdrawn by subject	1	1	1
Administrative decision	-	-	-
Death	2	1	-
Intolerable adverse event	1	-	-
Not specified	1	-	-
Lost to follow-up	1	-	1
Protocol deviation	-	-	3

Number of subjects in period 1[1]	Placebo
Started	38
Completed	33
Not completed	5
Consent withdrawn by subject	3
Administrative decision	1
Death	1
Intolerable adverse event	-
Not specified	-

Lost to follow-up	-
Protocol deviation	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 116 subjects were enrolled in the study; however, only 113 subjects were vaccinated.

Baseline characteristics

Reporting groups	
Reporting group title	50 µg + AlOH
Reporting group description:	
Subjects who received 3 injections of 50 µg ACAM-CDIFF vaccine plus aluminum hydroxide (AlOH) adjuvant administered on Days 0, 7, and 28.	
Reporting group title	100 µg
Reporting group description:	
Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine (no adjuvant) administered on Days 0, 7, and 28.	
Reporting group title	100 µg + AlOH
Reporting group description:	
Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine plus AlOH adjuvant administered on Days 0, 7, and 28.	
Reporting group title	Placebo
Reporting group description:	
Subjects who received 3 injections of placebo vaccine (0.9% normal saline) administered on Days 0, 7, and 28.	

Reporting group values	50 µg + AlOH	100 µg	100 µg + AlOH
Number of subjects	17	18	40
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	10	24
From 65-84 years	7	7	14
85 years and over	2	1	2
Age continuous Units: years			
arithmetic mean	62.1	61.7	59.5
standard deviation	± 21.4	± 15.6	± 18.6
Gender categorical Units: Subjects			
Female	12	13	28
Male	5	5	12

Reporting group values	Placebo	Total	
Number of subjects	38	113	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	

Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	21	63	
From 65-84 years	10	38	
85 years and over	7	12	
Age continuous			
Units: years			
arithmetic mean	65.6		
standard deviation	± 17.3	-	
Gender categorical			
Units: Subjects			
Female	24	77	
Male	14	36	

End points

End points reporting groups

Reporting group title	50 µg + AlOH
Reporting group description:	
Subjects who received 3 injections of 50 µg ACAM-CDIFF vaccine plus aluminum hydroxide (AlOH) adjuvant administered on Days 0, 7, and 28.	
Reporting group title	100 µg
Reporting group description:	
Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine (no adjuvant) administered on Days 0, 7, and 28.	
Reporting group title	100 µg + AlOH
Reporting group description:	
Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine plus AlOH adjuvant administered on Days 0, 7, and 28.	
Reporting group title	Placebo
Reporting group description:	
Subjects who received 3 injections of placebo vaccine (0.9% normal saline) administered on Days 0, 7, and 28.	

Primary: Number of Cases of Clostridium difficile Infection (CDI) Recurrence After A Third dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or a Placebo in Subjects with CDI

End point title	Number of Cases of Clostridium difficile Infection (CDI) Recurrence After A Third dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or a Placebo in Subjects with CDI[1]
End point description:	
A clostridium difficile infection (CDI) recurrence event must have satisfied the conditions of a CDI event and if the patient was on a recommended course of antibiotics, must have completed this and have been off these antibiotics for a minimum of 48 hours and must have had a minimum of 2 consecutive days without any diarrhea. Analysis was in the Per-protocol analysis set for efficacy. A CDI event was defined as: (i) passage of 3 or more loose stools within a 24 hour period (that conform to the shape of the container it is placed into), and (ii) a positive result of stool toxin testing using either ELISA/EIA or PCR, and (iii) absence of another identified cause for diarrhoea. In addition, a stool cytotoxicity assay was required to confirm positive ELISA results.	
End point type	Primary
End point timeframe:	
9-week period after the third dose of study vaccine. Days 29 to 91. Additional timepoints beyond Day 91 were collected and examined in other analyses.	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: The study was terminated early, therefore only descriptive analyses were performed. The original planned comparisons were not performed.	

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	9	10	20
Units: Number of cases				
number (not applicable)				
UK; -12 to 28	0	1	0	0
UK; 29 to 91	0	0	0	0
UK; -12 to 91	0	1	0	0

UK; 92 to 210	0	0	0	0
US; -12 to 28	1	0	1	1
US; 29 to 91	0	1	0	0
US; -12 to 91	1	1	1	1
US; 92 to 210	0	0	0	0
All; -12 to 28	1	1	1	1
All; 29 to 91	0	1	0	0
All; -12 to 91	1	2	1	1
All; 92 to 210	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentrations of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects Aged 18 to 64 years with Clostridium difficile Infection

End point title	Geometric Mean Concentrations of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects Aged 18 to 64 years with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin antibody enzyme-linked immunosorbent assay (ELISA). Analysis was in the Intent-to-treat analysis set for immunogenicity.

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	10	22	20
Units: Concentrations (EU/mL)				
geometric mean (confidence interval 95%)				
Toxin A IgG; Day 0	1.6 (0.64 to 4.02)	0.81 (0.68 to 0.96)	1.18 (0.72 to 1.91)	0.95 (0.69 to 1.3)
Toxin A IgG; Day 7	5.81 (0.68 to 49.96)	0.94 (0.67 to 1.33)	1.82 (0.83 to 4.03)	1.19 (0.79 to 1.79)
Toxin A IgG; Day 14	165.8 (11.93 to 2303.23)	7.09 (1.84 to 27.35)	8.62 (3.45 to 21.55)	1.27 (0.8 to 2.04)
Toxin A IgG; Day 28	190.8 (21.53 to 1690.7)	15.07 (3.23 to 70.25)	14.72 (5.97 to 36.28)	1.49 (0.74 to 3)
Toxin A IgG; Day 42	229.22 (47.77 to 1099.99)	40.32 (13.13 to 123.79)	104.93 (43.65 to 252.28)	1.1 (0.72 to 1.68)
Toxin A IgG; Day 91	98.64 (14.52 to 670.26)	25.11 (8.43 to 74.81)	36.13 (16.51 to 79.07)	1.58 (0.76 to 3.25)
Toxin A IgG; Day 210	25.53 (3.62 to 180.22)	8.76 (3.39 to 22.67)	13.14 (5.31 to 32.52)	1.4 (0.71 to 2.76)
Toxin B IgG; Day 0	4.12 (0.58 to 29.19)	0.72 (0.36 to 1.46)	1.84 (0.73 to 4.64)	1.66 (0.5 to 5.49)

Toxin B IgG; Day 7	5.88 (0.6 to 57.97)	0.76 (0.41 to 1.41)	5.22 (1.5 to 18.13)	2.32 (0.57 to 9.49)
Toxin B IgG; Day 14	52.4 (2.69 to 1018.7)	3.94 (0.43 to 36.03)	19.61 (4.64 to 82.92)	2.89 (0.63 to 13.22)
Toxin B IgG; Day 28	61.47 (3.88 to 974.48)	12.58 (2.21 to 71.46)	35.58 (11.58 to 109.31)	4.53 (0.99 to 20.8)
Toxin B IgG; Day 42	162.76 (31.41 to 843.4)	83.97 (26.15 to 269.59)	110.35 (46.24 to 263.36)	3.75 (0.81 to 17.32)
Toxin B IgG; Day 91	117.64 (37.08 to 373.21)	35.74 (10.39 to 123)	42.98 (17.39 to 106.21)	4.43 (1.1 to 17.9)
Toxin B IgG; Day 210	44.71 (8.21 to 243.47)	9.82 (1.93 to 50.02)	22.26 (8.33 to 59.51)	2.68 (0.75 to 9.52)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentrations of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects Aged 65 Years and Older with Clostridium difficile Infection

End point title	Geometric Mean Concentrations of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects Aged 65 Years and Older with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin antibody enzyme-linked immunosorbent assay (ELISA). Analysis was in the Intent-to-treat analysis set for immunogenicity.

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	7	15	14
Units: Concentrations (EU/mL)				
geometric mean (confidence interval 95%)				
Toxin A IgG; Day 0	0.75 (0.75 to 0.75)	0.75 (0.75 to 0.75)	0.75 (0.75 to 0.75)	1.11 (0.69 to 1.81)
Toxin A IgG; Day 7	0.75 (0.75 to 0.75)	0.91 (0.57 to 1.43)	0.81 (0.68 to 0.98)	1.48 (0.8 to 2.74)
Toxin A IgG; Day 14	2.43 (0.4 to 14.87)	10.86 (0.37 to 315.32)	2.23 (0.71 to 7.02)	1.53 (0.73 to 3.19)
Toxin A IgG; Day 28	7.28 (0.37 to 142.43)	18.84 (1.11 to 318.57)	6.25 (2.29 to 17.1)	1.49 (0.68 to 3.28)
Toxin A IgG; Day 42	31.61 (4.07 to 245.67)	170.61 (17.97 to 1619.81)	66.06 (28.72 to 151.96)	1.08 (0.55 to 2.15)
Toxin A IgG; Day 91	14 (1.87 to 104.85)	59.41 (7.89 to 447.4)	24.16 (10.56 to 55.27)	1.25 (0.65 to 2.38)
Toxin A IgG; Day 210	7.38 (0.88 to 61.54)	9.63 (1.05 to 88.11)	7.88 (3.15 to 19.72)	1.56 (0.73 to 3.32)

Toxin B IgG; Day 0	1.07 (0.1 to 11.06)	0.61 (0.31 to 1.2)	1.18 (0.54 to 2.58)	0.69 (0.28 to 1.68)
Toxin B IgG; Day 7	1.51 (0.13 to 17.68)	1.38 (0.24 to 8.02)	1.6 (0.65 to 3.93)	1.15 (0.37 to 3.55)
Toxin B IgG; Day 14	2.74 (0.14 to 54.12)	29.25 (0.73 to 1169.7)	5.63 (0.92 to 34.35)	1.28 (0.42 to 3.87)
Toxin B IgG; Day 28	4.07 (0.13 to 123.35)	116.3 (9.49 to 1424.82)	13.64 (3.24 to 57.48)	2.68 (0.68 to 10.62)
Toxin B IgG; Day 42	9.21 (0.52 to 163.49)	666.15 (140.53 to 3157.81)	56.76 (16.61 to 193.93)	2.57 (0.7 to 9.34)
Toxin B IgG; Day 91	5.28 (0.26 to 105.48)	177.31 (18.87 to 1666.38)	36.2 (12.04 to 108.84)	2.86 (0.71 to 11.57)
Toxin B IgG; Day 210	2.98 (0.21 to 42.34)	28.39 (3.39 to 237.67)	14.11 (4.3 to 46.35)	3.44 (0.86 to 13.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentrations of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Seropositive Subjects with Clostridium difficile Infection

End point title	Geometric Mean Concentrations of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Seropositive Subjects with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin antibody enzyme-linked immunosorbent assay (ELISA). Analysis was in the Intent-to-treat analysis set for immunogenicity.

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	17	37	34
Units: Concentrations (EU/mL)				
geometric mean (confidence interval 95%)				
Toxin A IgG; Day 0	3.41 (1.08 to 10.74)	1.6 (1.6 to 1.6)	8.87 (1.15 to 68.59)	3.87 (1.64 to 9.12)
Toxin A IgG; Day 7	23.32 (0.24 to 2297.32)	2.3 (2.3 to 2.3)	51.52 (7.97 to 332.91)	6.47 (3.25 to 12.86)
Toxin A IgG; Day 14	525.66 (23.3 to 11857.26)	10.2 (10.2 to 10.2)	203.72 (18.19 to 2281.77)	7.62 (2.94 to 19.75)
Toxin A IgG; Day 28	602.18 (39.21 to 9248.47)	15.3 (15.3 to 15.3)	183.01 (26.26 to 1275.53)	8.88 (2.12 to 37.26)
Toxin A IgG; Day 42	510.19 (38.17 to 6820.17)	48 (48 to 48)	247.09 (63.87 to 955.99)	8.34 (1.95 to 35.76)
Toxin A IgG; Day 91	147.29 (6.86 to 3163.8)	29.6 (29.6 to 29.6)	75.43 (12.71 to 447.79)	4.49 (1 to 20.17)

Toxin A IgG; Day 210	66.04 (21.25 to 205.19)	15.3 (15.3 to 15.3)	44.06 (12.17 to 159.52)	2.14 (0.59 to 7.85)
Toxin B IgG; Day 0	31.82 (2.54 to 397.99)	2.35 (1.31 to 4.24)	8.35 (3.68 to 18.97)	20.64 (2.77 to 153.99)
Toxin B IgG; Day 7	53.45 (4.11 to 695.1)	5.18 (0.92 to 29.13)	24.23 (9.4 to 62.47)	36.63 (3.06 to 437.96)
Toxin B IgG; Day 14	419.77 (88.9 to 1982.06)	490.33 (29.49 to 8153.86)	195.74 (66.48 to 576.3)	45.2 (3.85 to 530.79)
Toxin B IgG; Day 28	323.97 (123.46 to 850.11)	416.17 (28.89 to 5994.87)	177.96 (72.59 to 436.25)	34.61 (3.16 to 378.5)
Toxin B IgG; Day 42	352.72 (105.35 to 1180.89)	400.86 (34.57 to 4647.68)	230.69 (89.29 to 595.97)	35.39 (3.46 to 361.65)
Toxin B IgG; Day 91	144.87 (29.43 to 713.12)	270.84 (14.71 to 4987.99)	112.17 (48.8 to 257.81)	29.96 (3.5 to 256.11)
Toxin B IgG; Day 210	87.94 (16.51 to 468.43)	83.61 (7.58 to 922.53)	79.46 (34.56 to 182.67)	5.72 (0.69 to 47.46)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentrations of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Seronegative Subjects with Clostridium difficile Infection

End point title	Geometric Mean Concentrations of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Seronegative Subjects with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin antibody enzyme-linked immunosorbent assay (ELISA). Analysis was in the Intent-to-treat analysis set for immunogenicity.

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	17	37	34
Units: Concentrations (EU/mL)				
geometric mean (confidence interval 95%)				
Toxin A IgG; Day 0	0.75 (0.75 to 0.75)	0.75 (0.75 to 0.75)	0.75 (0.75 to 0.75)	0.75 (0.75 to 0.75)
Toxin A IgG; Day 7	0.9 (0.6 to 1.34)	0.88 (0.7 to 1.1)	0.82 (0.74 to 0.92)	0.86 (0.73 to 1)
Toxin A IgG; Day 14	6.11 (0.92 to 40.56)	8.21 (2.11 to 31.91)	3.22 (1.75 to 5.91)	0.85 (0.7 to 1.03)
Toxin A IgG; Day 28	14.74 (1.78 to 121.79)	16.46 (4.45 to 60.92)	7.54 (3.97 to 14.29)	1.05 (0.66 to 1.66)
Toxin A IgG; Day 42	45.06 (10.45 to 194.3)	66.66 (23.58 to 188.43)	84.39 (43.82 to 162.52)	0.79 (0.73 to 0.86)

Toxin A IgG; Day 91	20.64 (4.17 to 102.1)	35.05 (13.4 to 91.7)	29.18 (15.96 to 53.34)	1.16 (0.7 to 1.91)
Toxin A IgG; Day 210	9.04 (2.14 to 38.11)	8.77 (3.43 to 22.37)	9.56 (4.77 to 19.14)	1.3 (0.73 to 2.3)
Toxin B IgG; Day 0	0.4 (0.4 to 0.4)	0.4 (0.4 to 0.4)	0.4 (0.4 to 0.4)	0.4 (0.4 to 0.4)
Toxin B IgG; Day 7	0.51 (0.29 to 0.91)	0.49 (0.36 to 0.65)	0.6 (0.33 to 1.08)	0.48 (0.39 to 0.59)
Toxin B IgG; Day 14	1.08 (0.32 to 3.65)	1.31 (0.48 to 3.55)	1.3 (0.5 to 3.35)	0.52 (0.4 to 0.69)
Toxin B IgG; Day 28	1.83 (0.24 to 14)	8.62 (2.69 to 27.62)	4.71 (1.84 to 12.08)	1.28 (0.51 to 3.26)
Toxin B IgG; Day 42	8.13 (0.88 to 75.06)	108.24 (34.31 to 341.51)	41.35 (16.14 to 105.95)	1.15 (0.52 to 2.55)
Toxin B IgG; Day 91	4.6 (0.3 to 70.42)	34.1 (12.45 to 93.4)	18.65 (7.34 to 47.38)	1.6 (0.64 to 3.97)
Toxin B IgG; Day 210	2.98 (0.42 to 21.17)	6.36 (2.01 to 20.15)	6.67 (2.74 to 16.25)	2.03 (0.7 to 5.84)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Clostridium difficile Infection (CDI) Achieving Seroconversion After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo

End point title	Percentage of Subjects with Clostridium difficile Infection (CDI) Achieving Seroconversion After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin antibody enzyme-linked immunosorbent assay (ELISA). Seroconversion was defined as a minimum 2-fold and 4-fold increase in antibody levels for toxins A and B individually and the composite of A and B (a fold-rise achieved for both toxins A and B simultaneously) from baseline. Analysis was in the Intent-to-treat analysis set for immunogenicity.

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	7	9
Units: Percentage of subjects				
number (not applicable)				
Toxin A IgG; ≥2-fold rise Day 7/Day 0	20	0	14.3	11.1
Toxin A IgG; ≥2-fold rise Day 14/Day 0	60	66.7	71.4	0
Toxin A IgG; ≥2-fold rise Day 14/Day 7	60	66.7	57.1	0
Toxin A IgG; ≥2-fold rise Day 28/Day 0	60	83.3	71.4	0
Toxin A IgG; ≥2-fold rise Day 28/Day 7	60	83.3	71.4	0
Toxin A IgG; ≥2-fold rise Day 28/Day 14	40	50	28.6	0
Toxin A IgG; ≥2-fold rise Day 42/Day 0	100	100	100	0

Toxin A IgG; ≥2-fold rise Day 42/Day 28	60	83.3	85.7	0
Toxin A IgG; ≥2-fold rise Day 91/Day 0	100	100	100	0
Toxin A IgG; ≥2-fold rise Day 210/Day 0	80	80	85.7	0
Toxin A IgG; ≥4-fold rise Day 7/Day 0	0	0	0	0
Toxin A IgG; ≥4-fold rise Day 14/Day 0	60	66.7	71.4	0
Toxin A IgG; ≥4-fold rise Day 14/Day 7	60	66.7	57.1	0
Toxin A IgG; ≥4-fold rise Day 28/Day 0	60	83.3	71.4	0
Toxin A IgG; ≥4-fold rise Day 28/Day 7	60	83.3	57.1	0
Toxin A IgG; ≥4-fold rise Day 28/Day 14	40	33.3	28.6	0
Toxin A IgG; ≥4-fold rise Day 42/Day 0	100	83.3	100	0
Toxin A IgG; ≥4-fold rise Day 42/Day 28	40	66.7	42.9	0
Toxin A IgG; ≥4-fold rise Day 91/Day 0	80	100	100	0
Toxin A IgG; ≥4-fold rise Day 210/Day 0	80	60	85.7	0
Toxin B IgG; ≥2-fold rise Day 7/Day 0	20	16.7	28.6	22.2
Toxin B IgG; ≥2-fold rise Day 14/Day 0	60	33.3	71.4	22.2
Toxin B IgG; ≥2-fold rise Day 14/Day 7	40	33.3	42.9	0
Toxin B IgG; ≥2-fold rise Day 28/Day 0	40	83.3	85.7	33.3
Toxin B IgG; ≥2-fold rise Day 28/Day 7	40	83.3	71.4	33.3
Toxin B IgG; ≥2-fold rise Day 28/Day 14	20	66.7	28.6	33.3
Toxin B IgG; ≥2-fold rise Day 42/Day 0	60	100	100	33.3
Toxin B IgG; ≥2-fold rise Day 42/Day 28	40	83.3	42.9	0
Toxin B IgG; ≥2-fold rise Day 91/Day 0	60	100	100	22.2
Toxin B IgG; ≥2-fold rise Day 210/Day 0	60	80	85.7	22.2
Toxin B IgG; ≥4-fold rise Day 7/Day 0	20	16.7	14.3	0
Toxin B IgG; ≥4-fold rise Day 14/Day 0	40	33.3	42.9	0
Toxin B IgG; ≥4-fold rise Day 14/Day 7	20	33.3	28.6	0
Toxin B IgG; ≥4-fold rise Day 28/Day 0	40	83.3	85.7	22.2
Toxin B IgG; ≥4-fold rise Day 28/Day 7	40	83.3	57.1	11.1
Toxin B IgG; ≥4-fold rise Day 28/Day 14	20	66.7	28.6	11.1
Toxin B IgG; ≥4-fold rise Day 42/Day 0	60	100	100	33.3
Toxin B IgG; ≥4-fold rise Day 42/Day 28	20	66.7	42.9	0
Toxin B IgG; ≥4-fold rise Day 91/Day 0	60	83.3	85.7	11.1
Toxin B IgG; ≥4-fold rise Day 210/Day 0	60	80	71.4	22.2
Composite; ≥2-fold rise Day 7/Day 0	0	0	14.3	11.1
Composite; ≥2-fold rise Day 14/Day 0	40	33.3	57.1	0
Composite; ≥2-fold rise Day 14/Day 7	40	33.3	42.9	0
Composite; ≥2-fold rise Day 28/Day 0	40	83.3	57.1	0
Composite; ≥2-fold rise Day 28/Day 7	40	83.3	42.9	0
Composite; ≥2-fold rise Day 28/Day 14	20	50	14.3	0
Composite; ≥2-fold rise Day 42/Day 0	60	100	100	0
Composite; ≥2-fold rise Day 42/Day 28	20	66.7	28.6	0
Composite; ≥2-fold rise Day 91/Day 0	60	100	100	0
Composite; ≥2-fold rise Day 210/Day 0	60	80	71.4	0
Composite; ≥4-fold rise Day 7/Day 0	0	0	0	0

Composite; ≥4-fold rise Day 14/Day 0	40	33.3	42.9	0
Composite; ≥4-fold rise Day 14/Day 7	20	33.3	28.6	0
Composite; ≥4-fold rise Day 28/Day 0	40	83.3	57.1	0
Composite; ≥4-fold rise Day 28/Day 7	40	83.3	42.9	0
Composite; ≥4-fold rise Day 28/Day 14	20	33.3	14.3	0
Composite; ≥4-fold rise Day 42/Day 0	60	83.3	100	0
Composite; ≥4-fold rise Day 42/Day 28	0	33.3	28.6	0
Composite; ≥4-fold rise Day 91/Day 0	60	83.3	85.7	0
Composite; ≥4-fold rise Day 210/Day 0	60	60	57.1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects with Clostridium difficile Infection

End point title	Geometric Mean Titers of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin neutralization assay (TNA).

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	17	37	34
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Toxin A IgG; Day 0	17.1 (8.79 to 33.27)	10.23 (7.16 to 14.62)	14.69 (9.6 to 22.49)	12.82 (8.71 to 18.88)
Toxin A IgG; Day 7	32.59 (9.48 to 112.02)	13.99 (7.43 to 26.32)	19 (9.9 to 36.48)	15.8 (10.37 to 24.06)
Toxin A IgG; Day 14	216.92 (21.18 to 2221.38)	61.08 (13.99 to 266.65)	60.09 (26.16 to 138.05)	16.07 (10.62 to 24.31)
Toxin A IgG; Day 28	423.14 (47.53 to 3767.45)	68.07 (16.1 to 287.72)	79.1 (37.33 to 167.6)	15.91 (10.4 to 24.33)
Toxin A IgG; Day 42	718.52 (147.3 to 3504.82)	417.65 (127.58 to 1367.22)	435.3 (215.01 to 881.3)	14.02 (9.48 to 20.72)
Toxin A IgG; Day 91	481.56 (68.61 to 3379.94)	229.23 (90.78 to 578.81)	292.04 (152.26 to 560.13)	15.35 (9.76 to 24.15)
Toxin A IgG; Day 210	370.64 (85.97 to 1598)	197.44 (82.02 to 475.28)	300.49 (151.94 to 594.28)	17.38 (10.35 to 29.2)
Toxin B IgG; Day 0	44.26 (9.61 to 203.88)	11.26 (7.35 to 17.25)	21.28 (11.35 to 39.9)	16.82 (8.19 to 34.56)

Toxin B IgG; Day 7	56.95 (10.8 to 300.19)	14.35 (6.98 to 29.5)	35.13 (15.77 to 78.25)	22.44 (9.58 to 52.53)
Toxin B IgG; Day 14	169.39 (14.74 to 1946.03)	62.41 (9.72 to 400.84)	93.69 (28.86 to 304.13)	22.89 (9.62 to 54.47)
Toxin B IgG; Day 28	235.79 (16.13 to 3446.38)	54.82 (9.26 to 324.65)	84.95 (28.4 to 254.05)	27.16 (10.99 to 67.07)
Toxin B IgG; Day 42	300.63 (31.64 to 2856.16)	212.23 (44.07 to 1022.05)	141.29 (50.62 to 394.31)	20.36 (9.11 to 45.52)
Toxin B IgG; Day 91	237.06 (17.54 to 3204.1)	144.13 (36.98 to 561.74)	156.58 (63.82 to 384.18)	20.38 (9.62 to 43.19)
Toxin B IgG; Day 210	187.85 (21.85 to 1615.33)	162.81 (38.41 to 690.04)	171.3 (69.19 to 424.12)	30.32 (12.55 to 73.25)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects Aged 18 to 64 years with Clostridium difficile Infection

End point title	Geometric Mean Titers of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects Aged 18 to 64 years with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin neutralization assay (TNA).

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	10	22	20
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Toxin A; Day 0	36.15 (8.7 to 150.16)	12.14 (6.46 to 22.83)	16.34 (9.01 to 29.64)	10.92 (7.37 to 16.17)
Toxin A; Day 7	159.02 (11.93 to 2119.32)	17.25 (5.89 to 50.53)	25.28 (9.03 to 70.79)	12.56 (7.73 to 20.42)
Toxin A; Day 14	2968 (54.81 to 160713.4)	78.54 (9.97 to 618.67)	90.24 (26.99 to 301.71)	12.9 (7.71 to 21.57)
Toxin A; Day 28	1994.43 (58.42 to 68085.42)	114.21 (15.69 to 831.28)	108 (37.07 to 314.65)	13.69 (7.85 to 23.87)
Toxin A; Day 42	2903.43 (283.83 to 29700.12)	403.92 (76.98 to 2119.52)	545.33 (227.54 to 1306.93)	12.53 (7.61 to 20.61)
Toxin A; Day 91	2586.57 (58.47 to 114432.6)	255.74 (65.21 to 1003.03)	350.25 (153.83 to 797.45)	15.18 (7.88 to 29.24)

Toxin A; Day 210	844.29 (86.4 to 8250)	205.49 (55.98 to 754.32)	429.93 (183.37 to 1008.01)	15.42 (7.11 to 33.45)
Toxin B; Day 0	110.73 (11.36 to 1079.55)	12.77 (6.12 to 26.64)	26.14 (9.92 to 68.9)	20.34 (7.02 to 58.94)
Toxin B; Day 7	203.07 (13.29 to 3103.27)	13.36 (5.96 to 29.98)	51.98 (14.73 to 183.37)	24.11 (7.32 to 79.49)
Toxin B; Day 14	1550.93 (20.37 to 118083)	60.18 (4.28 to 846.11)	133.03 (23.33 to 758.68)	25.66 (7.28 to 90.43)
Toxin B; Day 28	1858.33 (20.27 to 170365.2)	52.09 (4.25 to 638.74)	123.47 (25.07 to 607.98)	27.07 (7.78 to 94.13)
Toxin B; Day 42	4201.6 (182.78 to 96582.08)	180 (20.57 to 1575.05)	252.09 (65.76 to 966.31)	25.3 (7.39 to 86.7)
Toxin B; Day 91	5226.74 (94.74 to 288340.9)	139.72 (18.74 to 1041.67)	223.76 (63.69 to 786.15)	26.06 (8.54 to 79.5)
Toxin B; Day 210	1554.39 (46.66 to 51777.55)	182.08 (20.69 to 1602.57)	298.34 (90.78 to 980.55)	31.32 (9.17 to 107.03)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects Aged 65 Years and Older with Clostridium difficile Infection

End point title	Geometric Mean Titers of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects Aged 65 Years and Older with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin neutralization assay (TNA).

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	7	15	14
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Toxin A; Day 0	9.75 (6.11 to 15.58)	8 (8 to 8)	12.43 (6.44 to 23.99)	16.41 (7.05 to 38.21)
Toxin A; Day 7	9.93 (5.96 to 16.54)	10.36 (5.5 to 19.53)	12.38 (6.52 to 23.48)	21.91 (9.83 to 48.81)
Toxin A; Day 14	23.04 (2.99 to 177.47)	40.17 (2.21 to 728.8)	32.65 (10.52 to 101.37)	21.65 (10.39 to 45.11)

Toxin A; Day 28	89.78 (3.88 to 2079.1)	28.73 (1.91 to 431.65)	50.09 (16.68 to 150.42)	20.18 (9.56 to 42.61)
Toxin A; Day 42	217.07 (22.36 to 2107.79)	446.52 (37.75 to 5282.22)	305.49 (81.86 to 1140.03)	16.59 (8.07 to 34.11)
Toxin A; Day 91	157.01 (11.55 to 2134.8)	191.01 (37.19 to 981.1)	226.42 (70.16 to 730.78)	15.63 (7.95 to 30.7)
Toxin A; Day 210	186.64 (15.84 to 2198.69)	185.94 (35.86 to 964.16)	173.18 (51.16 to 586.2)	21.14 (10.74 to 41.61)
Toxin B; Day 0	22.25 (1.98 to 249.97)	9.41 (6.32 to 14.02)	15.4 (7.8 to 30.42)	12.57 (4.7 to 33.64)
Toxin B; Day 7	21.95 (2.02 to 238.58)	15.9 (2.96 to 85.29)	19.52 (9.01 to 42.31)	20.25 (5.18 to 79.13)
Toxin B; Day 14	25.38 (1.5 to 428.18)	66.31 (1.76 to 2500.04)	55.38 (11.13 to 275.6)	19.6 (5.24 to 73.26)
Toxin B; Day 28	29.92 (1.01 to 888.05)	59.69 (1.75 to 2036.78)	49.08 (10.42 to 231.11)	27.29 (6.04 to 123.25)
Toxin B; Day 42	31.35 (2.53 to 388.47)	295.06 (10.28 to 8466.65)	56.88 (10.59 to 305.54)	14.7 (5.31 to 40.67)
Toxin B; Day 91	30.15 (1.78 to 511.7)	151.81 (13.4 to 1719.59)	94.99 (23.8 to 379.11)	13.81 (5.16 to 36.95)
Toxin B; Day 210	32.29 (2.5 to 417.64)	137.66 (10.14 to 1868.39)	72.96 (16.82 to 316.45)	28.74 (6.72 to 122.89)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Seropositive Subjects with Clostridium difficile Infection

End point title	Geometric Mean Titers of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Seropositive Subjects with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin neutralization assay (TNA).

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	10	6
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Toxin A; Day 0	67.09 (23.95 to 187.9)	64.51 (13.4 to 310.62)	123.31 (48.21 to 315.37)	107.11 (37.07 to 309.44)
Toxin A; Day 7	408.47 (58.97 to 2829.51)	210.86 (0 to 210.86)	352.01 (55.45 to 2234.71)	152.18 (72.38 to 319.96)

Toxin A; Day 14	19521.78 (3681.49 to 103517.8)	1163.36 (0 to 1163.36)	1097.28 (102.48 to 11748.58)	122.35 (56.47 to 265.12)
Toxin A; Day 28	17523.31 (10850.72 to 28299.17)	853.73 (0 to 853.73)	642.72 (76.32 to 5412.87)	85.91 (32.26 to 228.81)
Toxin A; Day 42	12976.13 (8976.73 to 18757.37)	1684.21 (0 to 1684.21)	2298.39 (486.15 to 10866.11)	85.2 (28.22 to 257.2)
Toxin A; Day 91	8599.81 (2154.22 to 34331.03)	825.84 (0 to 825.84)	926.01 (179.95 to 4765.23)	63.24 (13.87 to 288.37)
Toxin A; Day 210	3220.55 (2652.22 to 3910.65)	622.97 (4.98 to 77925.37)	1111.46 (183.57 to 6729.6)	29.47 (6.41 to 135.43)
Toxin B; Day 0	962.39 (73.17 to 12658.38)	55.63 (5.6 to 552.53)	270.87 (71.54 to 1025.52)	1081.15 (36.51 to 32019.8)
Toxin B; Day 7	1948.79 (256.3 to 14817.98)	219.52 (5.73 to 8415.53)	843.31 (242.91 to 2927.79)	2365.82 (96.07 to 58261.18)
Toxin B; Day 14	22395.3 (9272.01 to 54092.82)	43468.98 (6655.89 to 283891.6)	8115.79 (1427.12 to 46153.08)	2169.08 (90.05 to 52247.36)
Toxin B; Day 28	26898.48 (8155.45 to 88717.11)	30575 (2499.59 to 373993.2)	7944.79 (1437.14 to 43920.4)	2095.95 (83.9 to 52361.6)
Toxin B; Day 42	22981.2 (7006.12 to 75382)	20741.22 (2631.92 to 163454.2)	10200.68 (2361.41 to 44064.21)	1484.04 (87.83 to 25074.91)
Toxin B; Day 91	13121.43 (2070.41 to 83158.23)	10631.78 (334.25 to 338170.6)	4234.13 (907.02 to 19765.66)	1243.01 (92.03 to 16788.75)
Toxin B; Day 210	8086.41 (1454.09 to 44969.8)	12036.97 (390.54 to 370999.1)	4540.73 (1249.33 to 16503.45)	249.12 (16.64 to 3729.11)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Seronegative Subjects with Clostridium difficile Infection

End point title	Geometric Mean Titers of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Seronegative Subjects with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin neutralization assay (TNA).

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	14	28	28
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Toxin A; Day 0	8 (8 to 8)	8 (8 to 8)	8 (8 to 8)	8 (8 to 8)
Toxin A; Day 7	8 (8 to 8)	9.74 (7.24 to 13.1)	8 (8 to 8)	8.93 (7.87 to 10.13)
Toxin A; Day 14	13.03 (5.97 to 28.45)	40.09 (9.33 to 172.37)	25.41 (14.25 to 45.3)	9.38 (7.78 to 11.31)
Toxin A; Day 28	29.61 (8.55 to 102.53)	47.43 (10.7 to 210.21)	47.18 (23.31 to 95.5)	10.84 (7.54 to 15.57)
Toxin A; Day 42	117.76 (35.89 to 386.36)	337.01 (91.41 to 1242.56)	308.29 (149.76 to 634.62)	9.77 (7.58 to 12.59)
Toxin A; Day 91	70.48 (17.09 to 290.75)	190.88 (71.25 to 511.36)	234.15 (112.46 to 487.54)	11.69 (7.63 to 17.9)
Toxin A; Day 210	107.74 (21.82 to 531.92)	165.44 (61.77 to 443.11)	244.88 (115.83 to 517.72)	14.86 (8.11 to 27.21)
Toxin B; Day 0	8 (8 to 8)	8 (8 to 8)	8 (8 to 8)	8 (8 to 8)
Toxin B; Day 7	8 (8 to 8)	8 (8 to 8)	9.85 (7.02 to 13.82)	8 (8 to 8)
Toxin B; Day 14	8 (8 to 8)	13.78 (5.93 to 32.02)	15.73 (7.87 to 31.45)	8 (8 to 8)
Toxin B; Day 28	8 (8 to 8)	12.74 (6.15 to 26.4)	16.24 (8.94 to 29.48)	9.34 (7.37 to 11.83)
Toxin B; Day 42	20 (7.32 to 54.6)	67.5 (22.58 to 201.79)	35.87 (18.15 to 70.9)	8.63 (7.38 to 10.11)
Toxin B; Day 91	16.32 (4.4 to 60.57)	53.42 (22.11 to 129.08)	56.07 (27.22 to 115.49)	9.25 (7.42 to 11.52)
Toxin B; Day 210	21.88 (6.59 to 72.72)	55.52 (22.62 to 136.26)	65.28 (30.47 to 139.82)	15.83 (6.93 to 36.17)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Clostridium difficile Infection Reporting Solicited Injection Site or Systemic Reaction Following First Vaccination with Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or a Placebo

End point title	Percentage of Subjects with Clostridium difficile Infection Reporting Solicited Injection Site or Systemic Reaction Following First Vaccination with Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or a Placebo

End point description:

Solicited injection site: Pain, Redness, Swelling, Tenderness, and Itching. Solicited systemic reactions: Fever, Bowel movements, Loose/watery bowel, Abdominal pain, Vomiting, Appetite lost, Headache, Malaise, and Myalgia. Grade 3 Solicited Injection site reactions: Pain, Tenderness, and Itching – Significant, prevents daily activity; Redness and Swelling - >10 cm. Grade 3 Solicited systemic reactions: Fever - ≥39°C or ≥102.1°F; Bowel movements – not applicable; Loose/watery bowel - >6 loose/watery bowel movements; Abdominal pain, Vomiting, Appetite lost, Headache, Malaise, and Myalgia – Significant, prevents daily activities. Analysis was in the Safety analysis set.

End point type	Secondary

End point timeframe:
Day 0 (pre-injection) up to Day 6 post-injection 1

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	18	40	38
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	43.8	37.5	38.9	15.2
Grade 3 Injection site Pain	0	0	0	0
Injection site Redness	0	6.3	8.3	3
Grade 3 Injection site Redness	0	0	0	0
Injection site Swelling	0	0	8.3	3
Grade 3 Injection site Swelling	0	0	0	0
Injection site Tenderness	68.8	37.5	55.6	15.2
Grade 3 Injection site Tenderness	0	0	5.6	0
Injection site Itching	0	12.5	8.3	0
Grade 3 Injection site Itching	0	0	0	0
Fever	6.3	6.3	8.3	9.1
Grade 3 Fever	0	0	2.8	6.1
Bowel movements	100	100	100	97
Bowel movements; Yes	100	100	100	97
Loose/watery bowel	81.3	75	66.7	63.6
Grade 3 Loose/watery bowel	6.3	0	0	9.1
Abdominal pain	56.3	37.5	41.7	39.4
Grade 3 Abdominal pain	12.5	0	5.6	6.1
Vomiting	6.3	6.3	0	6.1
Grade 3 Vomiting	6.3	0	0	0
Appetite lost	31.3	6.3	19.4	15.2
Grade 3 Appetite lost	6.3	0	2.8	0
Headache	37.5	12.5	19.4	9.1
Grade 3 Headache	0	0	0	0
Malaise	6.3	6.3	19.4	18.2
Grade 3 Malaise	0	0	0	3
Myalgia	60	0	64.3	44.4
Grade 3 Myalgia	0	0	0	11.1

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Clostridium difficile Infection Reporting Solicited Injection Site or Systemic Reaction Following Second Vaccination with Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or a Placebo

End point title	Percentage of Subjects with Clostridium difficile Infection Reporting Solicited Injection Site or Systemic Reaction Following Second Vaccination with Clostridium Difficile Toxoid

	Vaccine (ACAM-CDIFFTM) or a Placebo

End point description:

Solicited injection site: Pain, Redness, Swelling, Tenderness, and Itching. Solicited systemic reactions: Fever, Bowel movements, Loose/watery bowel, Abdominal pain, Vomiting, Appetite lost, Headache, Malaise, and Myalgia. Grade 3 Solicited Injection site reactions: Pain, Tenderness, and Itching – Significant, prevents daily activity; Redness and Swelling - >10 cm. Grade 3 Solicited systemic reactions: Fever - ≥39°C or ≥102.1°F; Bowel movements – not applicable; Loose/watery bowel - >6 loose/watery bowel movements; Abdominal pain, Vomiting, Appetite lost, Headache, Malaise, and Myalgia – Significant, prevents daily activities. Analysis was in the Safety analysis set.

End point type	Secondary

End point timeframe:

Day 0 (pre-injection) up to Day 6 post-injection 2

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	34	37
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	33.3	37.5	44.1	6.5
Grade 3 Injection site Pain	0	0	8.8	3.2
Injection site Redness	0	18.8	5.9	0
Grade 3 Injection site Redness	0	0	0	0
Injection site Swelling	0	0	11.8	0
Grade 3 Injection site Swelling	0	0	0	0
Injection site Tenderness	60	43.8	52.9	6.5
Grade 3 Injection site Tenderness	0	0	2.9	0
Injection site Itching	6.7	12.5	8.8	0
Grade 3 Injection site Itching	0	0	0	0
Fever	6.7	12.5	2.9	6.3
Grade 3 Fever	0	0	2.9	3.1
Bowel movements	100	100	100	100
Bowel movements; Yes	100	100	100	100
Loose/watery bowel	40	87.5	58.8	62.5
Grade 3 Loose/watery bowel	6.7	6.3	2.9	3.1
Abdominal pain	46.7	43.8	41.2	34.4
Grade 3 Abdominal pain	13.3	6.3	5.9	3.1
Vomiting	6.7	0	5.9	6.3
Grade 3 Vomiting	6.7	0	0	3.1
Appetite lost	20	0	23.5	6.3
Grade 3 Appetite lost	6.7	0	2.9	0
Headache	46.7	18.8	20.6	9.4
Grade 3 Headache	6.7	0	2.9	3.1
Malaise	6.7	6.3	20.6	12.5
Grade 3 Malaise	6.7	0	0	0
Myalgia	40	50	64.3	42.9
Grade 3 Myalgia	20	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Clostridium difficile Infection Reporting Solicited Injection Site or Systemic Reaction Following Third Vaccination with Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or a Placebo

End point title	Percentage of Subjects with Clostridium difficile Infection Reporting Solicited Injection Site or Systemic Reaction Following Third Vaccination with Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or a Placebo

End point description:

Solicited injection site: Pain, Redness, Swelling, Tenderness, and Itching. Solicited systemic reactions: Fever, Bowel movements, Loose/watery bowel, Abdominal pain, Vomiting, Appetite lost, Headache, Malaise, and Myalgia. Grade 3 Solicited Injection site reactions: Pain, Tenderness, and Itching – Significant, prevents daily activity; Redness and Swelling - >10 cm. Grade 3 Solicited systemic reactions: Fever - ≥39°C or ≥102.1°F; Bowel movements – not applicable; Loose/watery bowel - >6 loose/watery bowel movements; Abdominal pain, Vomiting, Appetite lost, Headache, Malaise, and Myalgia – Significant, prevents daily activities. Analysis was in the Safety analysis set.

End point type	Secondary

End point timeframe:

Day 0 (pre-injection) up to Day 6 post-injection 3

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	16	33	32
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	25	43.8	39.4	3.1
Grade 3 Injection site Pain	0	0	0	0
Injection site Redness	8.3	18.8	15.2	0
Grade 3 Injection site Redness	0	0	3	0
Injection site Swelling	8.3	6.3	15.2	0
Grade 3 Injection site Swelling	0	0	6.1	0
Injection site Tenderness	33.3	50	51.5	9.4
Grade 3 Injection site Tenderness	0	0	6.1	0
Injection site Itching	16.7	0	12.1	3.1
Grade 3 Injection site Itching	0	0	0	0
Fever	0	0	6.1	6.3
Grade 3 Fever	0	0	3	0
Bowel movements	100	100	100	93.8
Bowel movements; Yes	100	100	100	93.8
Loose/watery bowel	41.7	50	33.3	37.5
Grade 3 Loose/watery bowel	0	6.3	0	3.1
Abdominal pain	41.7	43.8	36.4	15.6
Grade 3 Abdominal pain	8.3	6.3	6.1	3.1
Vomiting	16.7	0	6.1	0
Grade 3 Vomiting	8.3	0	0	0
Appetite lost	33.3	6.3	18.2	6.3
Grade 3 Appetite lost	8.3	0	3	0
Headache	16.7	6.3	18.2	9.4
Grade 3 Headache	0	0	3	0

Malaise	16.7	0	21.2	9.4
Grade 3 Malaise	0	0	3	0
Myalgia	20	0	71.4	30
Grade 3 Myalgia	20	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Fold Rise in Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects with Clostridium difficile Infection

End point title	Geometric Mean Fold Rise in Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin antibody enzyme-linked immunosorbent assay (ELISA). Analysis was in the Intent-to-treat analysis set for immunogenicity.

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	17	37	34
Units: Concentrations (EU/mL)				
geometric mean (confidence interval 95%)				
Toxin A IgG; Day 7/Day 0	1.65 (0.92 to 2.99)	1.09 (0.98 to 1.21)	1.25 (0.95 to 1.65)	1.15 (0.98 to 1.35)
Toxin A IgG; Day 14/Day 0	11.66 (2.43 to 55.93)	6.86 (2.18 to 21.55)	3.72 (2.18 to 6.37)	1.21 (0.98 to 1.47)
Toxin A IgG; Day 14/Day 7	6.78 (1.85 to 24.82)	6.26 (2.15 to 18.22)	3.01 (1.86 to 4.88)	1.05 (0.95 to 1.16)
Toxin A IgG; Day 28/Day 0	24.06 (5.02 to 115.4)	12.39 (4.03 to 38.06)	6.86 (4.01 to 11.73)	1.39 (0.95 to 2.02)
Toxin A IgG; Day28/Day 7	13.37 (3.3 to 54.21)	11.31 (3.91 to 32.72)	5.66 (3.35 to 9.56)	1.18 (0.9 to 1.55)
Toxin A IgG; Day 28/Day 14	1.76 (0.95 to 3.28)	1.81 (1.15 to 2.85)	1.84 (1.21 to 2.81)	1.1 (0.87 to 1.38)
Toxin A IgG; Day 42/Day 0	45.9 (15.32 to 137.51)	43.29 (16.54 to 113.29)	52.96 (29.41 to 95.35)	1.13 (0.94 to 1.37)
Toxin A IgG; Day 42/Day 28	2.17 (0.92 to 5.12)	3.48 (1.76 to 6.87)	6.98 (4.13 to 11.78)	0.94 (0.88 to 1.01)
Toxin A IgG; Day 91/Day 0	19.02 (5.84 to 61.93)	24.05 (10.37 to 55.79)	19.9 (11.76 to 33.67)	1.33 (0.89 to 1.99)
Toxin A IgG; Day 210/Day 0	8.65 (3.04 to 24.61)	6.62 (3.01 to 14.57)	7.69 (4.43 to 13.34)	1.26 (0.82 to 1.96)
Toxin B IgG; Day 7/Day 0	1.35 (1.02 to 1.77)	1.33 (0.86 to 2.07)	1.91 (1.21 to 3.02)	1.25 (0.92 to 1.71)

Toxin B IgG; Day 14/Day 0	4.23 (1.72 to 10.39)	9.66 (2.43 to 38.48)	6.7 (3.13 to 14.35)	1.39 (0.99 to 1.95)
Toxin B IgG; Day 14/Day 7	3.07 (1.44 to 6.58)	7.12 (2.16 to 23.4)	3.56 (2.03 to 6.23)	1.1 (0.98 to 1.24)
Toxin B IgG; Day 28/Day 0	5.37 (1.74 to 16.52)	26.98 (8.62 to 84.5)	11.48 (5.93 to 22.22)	2.25 (1.18 to 4.27)
Toxin B IgG; Day 28/Day 7	3.8 (1.44 to 10.02)	19.87 (7.63 to 51.76)	6.02 (3.49 to 10.38)	1.69 (0.98 to 2.9)
Toxin B IgG; Day 28/Day 14	1.23 (0.74 to 2.04)	2.79 (1.53 to 5.11)	1.71 (1.2 to 2.45)	1.52 (0.93 to 2.48)
Toxin B IgG; Day 42/Day 0	11.69 (3.46 to 39.49)	146.08 (57.98 to 368.05)	40.05 (20.49 to 78.27)	2.1 (1.19 to 3.71)
Toxin B IgG; Day 42/Day 28	2.25 (1.06 to 4.77)	6.03 (2.13 to 17.06)	3.21 (1.97 to 5.22)	1.13 (0.93 to 1.37)
Toxin B IgG; Day 91/Day 0	5.47 (1.33 to 22.44)	58.14 (22.42 to 150.75)	19.08 (9.84 to 36.98)	2.49 (1.28 to 4.84)
Toxin B IgG; Day 210/Day 0	3.7 (1.15 to 11.91)	13.72 (5.39 to 34.93)	9.33 (5.14 to 16.95)	1.77 (0.75 to 4.16)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentrations of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects with Clostridium difficile Infection

End point title	Geometric Mean Concentrations of Anti-toxin A and B IgG After A Third Dose of Clostridium Difficile Toxoid Vaccine (ACAM-CDIFFTM) or A Placebo in Subjects with Clostridium difficile Infection

End point description:

Anti-toxin A and B IgG antibodies were detected using toxin antibody enzyme-linked immunosorbent assay (ELISA). Analysis was in the Intent-to-treat analysis set for efficacy.

End point type	Secondary

End point timeframe:

Day 0, 7, 14, 28, 42, 91, and 210

End point values	50 µg + AlOH	100 µg	100 µg + AlOH	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	17	37	34
Units: Concentrations (EU/mL)				
geometric mean (confidence interval 95%)				
Toxin A IgG; Day 0	1.04 (0.7 to 1.53)	0.78 (0.71 to 0.86)	0.99 (0.73 to 1.33)	1.01 (0.78 to 1.3)
Toxin A IgG; Day 7	1.8 (0.7 to 4.68)	0.93 (0.73 to 1.18)	1.32 (0.82 to 2.14)	1.3 (0.94 to 1.81)
Toxin A IgG; Day 14	17.07 (2.69 to 108.18)	8.32 (2.35 to 29.41)	5.1 (2.49 to 10.43)	1.38 (0.93 to 2.03)
Toxin A IgG; Day 28	37.26 (5.83 to 238.2)	16.39 (4.86 to 55.3)	10.4 (5.39 to 20.06)	1.49 (0.91 to 2.46)

Toxin A IgG; Day 42	78.88 (22.06 to 282.02)	65.21 (24.93 to 170.59)	87.65 (47.97 to 160.16)	1.1 (0.78 to 1.54)
Toxin A IgG; Day 91	30.58 (7.95 to 117.56)	34.68 (14.18 to 84.82)	30.55 (17.66 to 52.86)	1.44 (0.89 to 2.34)
Toxin A IgG; Day 210	12.97 (3.72 to 45.21)	9.1 (3.81 to 21.71)	10.75 (5.73 to 20.17)	1.46 (0.9 to 2.36)
Toxin B IgG; Day 0	1.91 (0.46 to 7.86)	0.67 (0.43 to 1.05)	1.54 (0.83 to 2.87)	1.17 (0.54 to 2.57)
Toxin B IgG; Day 7	2.7 (0.59 to 12.43)	0.97 (0.48 to 1.97)	3.26 (1.44 to 7.38)	1.74 (0.7 to 4.33)
Toxin B IgG; Day 14	10.69 (1.46 to 78.49)	8.35 (1.44 to 48.39)	12.07 (4.06 to 35.89)	2.04 (0.79 to 5.31)
Toxin B IgG; Day 28	15.81 (2.13 to 117.54)	28.96 (7.31 to 114.75)	24.12 (10.25 to 56.77)	3.7 (1.33 to 10.29)
Toxin B IgG; Day 42	34.67 (6.22 to 193.19)	167.46 (62.38 to 449.54)	85.21 (42.95 to 169.05)	3.22 (1.19 to 8.75)
Toxin B IgG; Day 91	18.27 (2.66 to 125.7)	65.16 (22.59 to 187.95)	40.01 (20.61 to 77.69)	3.74 (1.43 to 9.77)
Toxin B IgG; Day 210	10.2 (1.98 to 52.49)	15.01 (4.75 to 47.45)	18.6 (9.05 to 38.22)	2.94 (1.21 to 7.17)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse event data were collected from Day 0 to Day 91 after the first vaccination.	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1
Reporting groups	
Reporting group title	50 µg + AlOH
Reporting group description:	
Subjects who received 3 injections of 50 µg ACAM-CDIFF vaccine plus aluminum hydroxide (AlOH) adjuvant (400 µg aluminum per dose) administered on Days 0, 7, and 28.	
Reporting group title	100 µg
Reporting group description:	
Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine (no adjuvant) administered on Days 0, 7, and 28.	
Reporting group title	100 µg + AlOH
Reporting group description:	
Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine plus AlOH adjuvant (400 µg aluminum per dose) administered on Days 0, 7, and 28.	
Reporting group title	Placebo
Reporting group description:	
Subjects who received 3 injections of placebo vaccine (0.9% normal saline) administered on Days 0, 7, and 28.	

Serious adverse events	50 µg + AlOH	100 µg	100 µg + AlOH
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 17 (52.94%)	3 / 18 (16.67%)	12 / 40 (30.00%)
number of deaths (all causes)	3	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			

Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stenosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood potassium increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Graft thrombosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ulna fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft occlusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Complex partial seizures			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute abdomen			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess fungal			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary sepsis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter related infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cellulitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	2 / 17 (11.76%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis pseudomonas			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	3 / 40 (7.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Postoperative wound infection			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 38 (34.21%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			

subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular stenosis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcoholism			

subjects affected / exposed	1 / 38 (2.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood potassium increased				
subjects affected / exposed	1 / 38 (2.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Graft thrombosis				
subjects affected / exposed	1 / 38 (2.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 38 (2.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Incisional hernia				
subjects affected / exposed	1 / 38 (2.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Multiple fractures				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ulna fracture				
subjects affected / exposed	1 / 38 (2.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular graft occlusion				
subjects affected / exposed	1 / 38 (2.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Cystic fibrosis lung				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 38 (2.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure congestive				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Complex partial seizures				

subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute abdomen			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulum			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess fungal			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Biliary sepsis			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Catheter related infection			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridial infection			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gangrene			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis pseudomonas			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Implant site infection			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	50 µg + AlOH	100 µg	100 µg + AlOH
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 17 (94.12%)	16 / 18 (88.89%)	36 / 40 (90.00%)
General disorders and administration site conditions			
Discomfort			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	1 / 40 (2.50%)
occurrences (all)	1	1	1

Fatigue			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	3	0
Injection site erythema			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Injection site haematoma			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Injection site induration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Injection site warmth			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Multi-organ failure			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 18 (0.00%)	3 / 40 (7.50%)
occurrences (all)	2	0	3
Vaccination site pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed[1]	7 / 16 (43.75%)	7 / 16 (43.75%)	15 / 34 (44.12%)
occurrences (all)	7	7	15
Injection site redness			
alternative assessment type: Systematic			
subjects affected / exposed[2]	1 / 12 (8.33%)	3 / 16 (18.75%)	5 / 33 (15.15%)
occurrences (all)	1	3	5
Injection site swelling			

alternative assessment type: Systematic			
subjects affected / exposed[3]	1 / 12 (8.33%)	1 / 16 (6.25%)	5 / 33 (15.15%)
occurrences (all)	1	1	5
Injection site tenderness			
alternative assessment type: Systematic			
subjects affected / exposed[4]	11 / 16 (68.75%)	8 / 16 (50.00%)	20 / 36 (55.56%)
occurrences (all)	11	8	20
Injection site itching			
alternative assessment type: Systematic			
subjects affected / exposed[5]	2 / 12 (16.67%)	2 / 16 (12.50%)	4 / 33 (12.12%)
occurrences (all)	2	2	4
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[6]	1 / 15 (6.67%)	2 / 16 (12.50%)	3 / 36 (8.33%)
occurrences (all)	1	2	3
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed[7]	9 / 16 (56.25%)	7 / 16 (43.75%)	15 / 36 (41.67%)
occurrences (all)	9	7	15
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed[8]	2 / 12 (16.67%)	1 / 16 (6.25%)	7 / 33 (21.21%)
occurrences (all)	2	1	7
Reproductive system and breast disorders			
Nipple pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	2 / 40 (5.00%)
occurrences (all)	0	1	2

Pleural effusion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Insomnia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Restlessness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram change			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Atrial fibrillation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Cardiac failure congestive			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	3
Tremor			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0

Headache			
alternative assessment type: Systematic			
subjects affected / exposed[9]	7 / 15 (46.67%)	3 / 16 (18.75%)	7 / 34 (20.59%)
occurrences (all)	7	3	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Crohn's disease			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	2 / 17 (11.76%)	0 / 18 (0.00%)	7 / 40 (17.50%)
occurrences (all)	4	0	9
Haematochezia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Haemorrhoids			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Intestinal obstruction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	5 / 40 (12.50%)
occurrences (all)	2	0	6

Oral pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Proctalgia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Bowel movements			
alternative assessment type: Systematic			
subjects affected / exposed[10]	16 / 16 (100.00%)	16 / 16 (100.00%)	36 / 36 (100.00%)
occurrences (all)	16	16	36
Loose/watery bowel			
alternative assessment type: Systematic			
subjects affected / exposed[11]	13 / 16 (81.25%)	14 / 16 (87.50%)	24 / 36 (66.67%)
occurrences (all)	13	14	24
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed[12]	2 / 12 (16.67%)	1 / 16 (6.25%)	2 / 33 (6.06%)
occurrences (all)	2	1	2
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	3 / 17 (17.65%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences (all)	3	0	1
Skin ulcer			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Urinary retention			

subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Back pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	3 / 40 (7.50%)
occurrences (all)	0	1	3
Rotator cuff syndrome			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed[13]	3 / 5 (60.00%)	1 / 2 (50.00%)	10 / 14 (71.43%)
occurrences (all)	3	1	10
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Catheter related infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Clostridial infection			
subjects affected / exposed	2 / 17 (11.76%)	0 / 18 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	1
Ear infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	1 / 40 (2.50%)
occurrences (all)	1	1	1
Nasopharyngitis			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	3
Oral candidiasis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	4 / 40 (10.00%)
occurrences (all)	0	2	6
Rhinitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Septic shock			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	2 / 17 (11.76%)	2 / 18 (11.11%)	7 / 40 (17.50%)
occurrences (all)	2	3	8
Urinary tract infection fungal			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 17 (11.76%)	3 / 18 (16.67%)	2 / 40 (5.00%)
occurrences (all)	4	3	2
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	3 / 40 (7.50%)
occurrences (all)	2	0	3
Metabolic acidosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Appetite lost			
alternative assessment type: Systematic			
subjects affected / exposed[14]	4 / 12 (33.33%)	1 / 16 (6.25%)	8 / 34 (23.53%)
occurrences (all)	4	1	8

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 38 (84.21%)		
General disorders and administration site conditions			
Discomfort			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	9		
Fatigue			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Injection site erythema			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Injection site haematoma			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Injection site induration			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Injection site warmth			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Multi-organ failure			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		

Vaccination site pain				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Injection site pain				
alternative assessment type: Systematic				
subjects affected / exposed[1]	5 / 33 (15.15%)			
occurrences (all)	5			
Injection site redness				
alternative assessment type: Systematic				
subjects affected / exposed[2]	1 / 33 (3.03%)			
occurrences (all)	1			
Injection site swelling				
alternative assessment type: Systematic				
subjects affected / exposed[3]	1 / 33 (3.03%)			
occurrences (all)	1			
Injection site tenderness				
alternative assessment type: Systematic				
subjects affected / exposed[4]	5 / 33 (15.15%)			
occurrences (all)	5			
Injection site itching				
alternative assessment type: Systematic				
subjects affected / exposed[5]	1 / 32 (3.13%)			
occurrences (all)	1			
Fever				
alternative assessment type: Systematic				
subjects affected / exposed[6]	3 / 33 (9.09%)			
occurrences (all)	3			
Abdominal pain				
alternative assessment type: Systematic				
subjects affected / exposed[7]	13 / 33 (39.39%)			
occurrences (all)	13			
Malaise				
alternative assessment type: Systematic				

subjects affected / exposed[8]	6 / 33 (18.18%)		
occurrences (all)	6		
Reproductive system and breast disorders			
Nipple pain			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Restlessness			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Electrocardiogram change			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Atrial fibrillation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Cardiac failure congestive			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Headache			
alternative assessment type: Systematic			
subjects affected / exposed[9]	3 / 32 (9.38%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Crohn's disease			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		

Diarrhoea				
subjects affected / exposed	3 / 38 (7.89%)			
occurrences (all)	6			
Haematochezia				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Haemorrhoids				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Intestinal obstruction				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	3 / 38 (7.89%)			
occurrences (all)	3			
Oral pain				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Proctalgia				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Rectal haemorrhage				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Bowel movements				
alternative assessment type: Systematic				
subjects affected / exposed[10]	32 / 32 (100.00%)			
occurrences (all)	32			
Loose/watery bowel				
alternative assessment type: Systematic				
subjects affected / exposed[11]	21 / 33 (63.64%)			
occurrences (all)	21			
Vomiting				
alternative assessment type: Systematic				

subjects affected / exposed[12]	2 / 32 (6.25%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Skin ulcer			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Urinary retention			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed[13]	4 / 9 (44.44%)		
occurrences (all)	4		
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Catheter related infection				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Cellulitis				
subjects affected / exposed	2 / 38 (5.26%)			
occurrences (all)	2			
Clostridial infection				
subjects affected / exposed	1 / 38 (2.63%)			
occurrences (all)	1			
Ear infection				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection				
subjects affected / exposed	3 / 38 (7.89%)			
occurrences (all)	3			
Nasopharyngitis				
subjects affected / exposed	2 / 38 (5.26%)			
occurrences (all)	2			
Oral candidiasis				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Septic shock				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Staphylococcal bacteraemia				
subjects affected / exposed	0 / 38 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				

subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		
Urinary tract infection fungal			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	7		
Hypokalaemia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	4		
Metabolic acidosis			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Appetite lost			
alternative assessment type: Systematic			
subjects affected / exposed[14]	5 / 33 (15.15%)		
occurrences (all)	5		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination;

the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2008	Suspected unexpected serious adverse events and their definitions were added.
06 February 2009	Primary end point updated to compare the event rate of CDI in groups assigned to ACAM-CDIFF vaccine (pooled groups) versus placebo in the 9-week period after the third dose of study vaccine (Study Days 29 to 91) in subjects with a first episode of laboratory confirmed CDI up to 10 days prior to the first dose of study vaccine, receiving antibiotic standard of care; safety endpoint updated to compare the frequency of local and systemic adverse events (AEs) and serious adverse events (SAEs), new laboratory abnormalities, reported in subjects assigned to ACAM-CDIFF vaccine (pooled) versus placebo since first dose of study vaccine until day 210; clarified definition to "a change in bowel habit with passage of 2 or more loose stools within 24 hours (that conforms to the shape of the container it is placed into)"; exclusion criteria were revised; an Independent Data Monitoring Committee (IDMC) was added at the request of FDA to ensure increase safety monitoring; added that a related fatal event would trigger an immediate pause of the study and investigation by the IDMC; Clarification about treatment and documentation of CDI recurrences; Replaced a structured interview with questions about symptoms of CDI and AEs through Day 210; Revised definition of causal relationship to study vaccination and toxicity grading scale for local site reactions and systemic reactions. Two interim analyses were proposed.
31 March 2009	Added that a confirmatory cytotoxicity assay test was required for inclusion and viral serology tests HBsAg and HCV were removed from the study.
06 May 2009	Number of clinical sites increased from 70 to 75; increased screening period to within 12 days of administration of the first dose and definition of Clostridium difficile Infection (CDI) refined to: "Primary CDI redefined; modified age range of subjects to allow all adults ≥ 18 years; the cytotoxin assay was defined more clearly; modified/revised some exclusion criteria on: expected mortality, previous CDI events, platelet counts, previous chemotherapy, body mass index, time for completion. Added detailed information concerning the Independent Data Monitoring Committee and their review of safety information; and a proposal for 3 interim analyses in the study.
15 June 2009	Modified exclusion criterion describing platelet counts (specifically, count should not be < 70,000 cell/mm3).
20 August 2009	Extended study period to 1.5 years; added a secondary objective; reduced overall study number to 612 subjects, reduced power to 80%, and based on Fisher exact test; changed screening tests to ELISA/EIA or PCR, with cytotoxicity as a confirmatory test; applied randomization and analysis by country; added a rationale for the primary objective; adjusted the clinical diagnostic criteria to be more stringent, in accordance with national guidelines, modified or added 3 exclusion criteria. Added calculation of BMI; clarified reporting of serious adverse events; and replaced the Toxicity Grading Scale for solicited reactions with the one used by Sanofi Pasteur.
19 November 2009	Added geometric mean titers to the immunogenicity evaluations and allowed pneumococcal vaccine within 30 days before or after trial vaccination.
30 April 2010	Stopped enrollment in the UK; changed the statistical method to the Fisher exact test for comparison of the CDI event rates; changed analysis of seroconversion from Chi-Square or Fisher test to the Newcombe-Wilson without continuity correction; revised inclusion and exclusion criteria; and specified that the second IDMC meeting would occur after the first 38 subjects were enrolled and received 2 doses of vaccine.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 December 2010	This study was halted due to operational futility before the planned number of subjects was enrolled. Significant efforts were made by the Sponsor to facilitate enrollment with the study sites, including amending the protocol to relax inclusion/exclusion criteria based on screening failures and discussion with key opinion leaders, amending the protocol to use paper diaries in place of the e-diaries, and facilitating communication with investigators and site staff. Despite these efforts, subject accrual remained low and enrollment metrics were not met. Ultimately, the decision was made to terminate subject enrollment.	-

Notes:

Limitations and caveats

None reported