



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 + AIOH |

Arm description:

Subjects who received 3 injections of 50 µg ACAM-CDIFF vaccine plus aluminum hydroxide (AIOH) 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 + AIOH |
|------------------|---------------|

Arm description:

Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine plus AIOH 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 + AIOH | 100 µg | 100 µg + AIOH |
|---|--------------|--------|---------------|
| 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 + AIOH |
| Reporting group description: Subjects who received 3 injections of 50 µg ACAM-CDIFF vaccine plus aluminum hydroxide (AIOH) 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 + AIOH |
| Reporting group description: Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine plus AIOH 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 + AIOH | 100 µg | 100 µg + AIOH |
|--|--------------|--------|---------------|
| 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 + AIOH |
| Reporting group description: Subjects who received 3 injections of 50 µg ACAM-CDIFF vaccine plus aluminum hydroxide (AIOH) 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 + AIOH |
| Reporting group description: Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine plus AIOH 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH | 100 µg | 100 µg + AIOH | 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; \geq 4-fold rise Day 14/Day 0 | 40 | 33.3 | 42.9 | 0 |
| Composite; \geq 4-fold rise Day 14/Day 7 | 20 | 33.3 | 28.6 | 0 |
| Composite; \geq 4-fold rise Day 28/Day 0 | 40 | 83.3 | 57.1 | 0 |
| Composite; \geq 4-fold rise Day 28/Day 7 | 40 | 83.3 | 42.9 | 0 |
| Composite; \geq 4-fold rise Day 28/Day 14 | 20 | 33.3 | 14.3 | 0 |
| Composite; \geq 4-fold rise Day 42/Day 0 | 60 | 83.3 | 100 | 0 |
| Composite; \geq 4-fold rise Day 42/Day 28 | 0 | 33.3 | 28.6 | 0 |
| Composite; \geq 4-fold rise Day 91/Day 0 | 60 | 83.3 | 85.7 | 0 |
| Composite; \geq 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH | 100 µg | 100 µg + AIOH | 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 - $\geq 39^{\circ}\text{C}$ or $\geq 102.1^{\circ}\text{F}$; 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 + AIOH | 100 µg | 100 µg + AIOH | 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 |
|-----------------|--|

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 - $\geq 39^{\circ}\text{C}$ or $\geq 102.1^{\circ}\text{F}$; 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 + AIOH | 100 µg | 100 µg + AIOH | 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 - $\geq 39^{\circ}\text{C}$ or $\geq 102.1^{\circ}\text{F}$; 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH | 100 µg | 100 µg + AIOH | 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 + AIOH |
|-----------------------|--------------|

Reporting group description:

Subjects who received 3 injections of 50 µg ACAM-CDIFF vaccine plus aluminum hydroxide (AIOH) 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 + AIOH |
|-----------------------|---------------|

Reporting group description:

Subjects who received 3 injections of 100 µg ACAM-CDIFF Vaccine plus AIOH 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 + AIOH | 100 µg | 100 µg + AIOH |
|---|-----------------|-----------------|------------------|
| 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 + AIOH | 100 µg | 100 µg + AIOH |
|---|------------------|------------------|------------------|
| 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] occurrences (all) | 1 / 12 (8.33%) 1 | 1 / 16 (6.25%) 1 | 5 / 33 (15.15%) 5 |
| Injection site tenderness alternative assessment type: Systematic subjects affected / exposed ^[4] occurrences (all) | 11 / 16 (68.75%) 11 | 8 / 16 (50.00%) 8 | 20 / 36 (55.56%) 20 |
| Injection site itching alternative assessment type: Systematic subjects affected / exposed ^[5] occurrences (all) | 2 / 12 (16.67%) 2 | 2 / 16 (12.50%) 2 | 4 / 33 (12.12%) 4 |
| Fever alternative assessment type: Systematic subjects affected / exposed ^[6] occurrences (all) | 1 / 15 (6.67%) 1 | 2 / 16 (12.50%) 2 | 3 / 36 (8.33%) 3 |
| Abdominal pain alternative assessment type: Systematic subjects affected / exposed ^[7] occurrences (all) | 9 / 16 (56.25%) 9 | 7 / 16 (43.75%) 7 | 15 / 36 (41.67%) 15 |
| Malaise alternative assessment type: Systematic subjects affected / exposed ^[8] occurrences (all) | 2 / 12 (16.67%) 2 | 1 / 16 (6.25%) 1 | 7 / 33 (21.21%) 7 |
| Reproductive system and breast disorders Nipple pain subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 40 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | 2 / 40 (5.00%) 2 |

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

| | | | |
|---|----------------------|----------------------|----------------------|
| Headache alternative assessment type: Systematic subjects affected / exposed ^[9] occurrences (all) | 7 / 15 (46.67%) 7 | 3 / 16 (18.75%) 3 | 7 / 34 (20.59%) 7 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 18 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 40 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Colitis subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | 1 / 40 (2.50%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 18 (0.00%) 0 | 3 / 40 (7.50%) 3 |
| Crohn's disease subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 40 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 4 | 0 / 18 (0.00%) 0 | 7 / 40 (17.50%) 9 |
| Haematochezia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Haemorrhoids subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 40 (0.00%) 0 |
| Intestinal obstruction subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 2 | 0 / 18 (0.00%) 0 | 5 / 40 (12.50%) 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 occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | 0 / 40 (0.00%) 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] occurrences (all) | 4 / 12 (33.33%) 4 | 1 / 16 (6.25%) 1 | 8 / 34 (23.53%) 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] occurrences (all) | 6 / 33 (18.18%) 6 | | |
| Reproductive system and breast disorders Nipple pain subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) | 1 / 38 (2.63%) 1 0 / 38 (0.00%) 0 0 / 38 (0.00%) 0 | | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Restlessness subjects affected / exposed occurrences (all) | 1 / 38 (2.63%) 1 0 / 38 (0.00%) 0 0 / 38 (0.00%) 0 | | |
| Investigations Blood glucose increased subjects affected / exposed occurrences (all) Electrocardiogram change subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 0 / 38 (0.00%) 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] occurrences (all) | 2 / 32 (6.25%) 2 | | |
| Skin and subcutaneous tissue disorders Blister subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Skin ulcer subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 0 / 38 (0.00%) 0 0 / 38 (0.00%) 0 | | |
| Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) Urinary retention subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 0 / 38 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Rotator cuff syndrome subjects affected / exposed occurrences (all) Myalgia alternative assessment type: Systematic subjects affected / exposed ^[13] occurrences (all) | 0 / 38 (0.00%) 0 0 / 38 (0.00%) 0 0 / 38 (0.00%) 0 4 / 9 (44.44%) 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/mm ³). |
| 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