Clinical trial results:
DOSE-CONFIRMATION, IMMUNOGENICITY AND SAFETY STUDY OF THE CLOSTRIDIUM DIFFICILE VACCINE CANDIDATE VLA84 IN HEALTHY ADULTS AGED 50 YEARS AND OLDER. RANDOMIZED, CONTROLLED, OBSERVER-BLIND PHASE II STUDY.

Summary

EudraCT number	2014-003934-22
Trial protocol	DE
Global end of trial date	15 October 2015

Results information

Result version number	v1 (current)
This version publication date	19 January 2017
First version publication date	19 January 2017

Trial information

Trial identification

Sponsor protocol code	VLA84-201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Valneva Austria GmbH
Sponsor organisation address	Campus Vienna Biocenter 3, Vienna, Austria, 1030
Public contact	Clinical Operations, Valneva Austria GmbH, 0043 1206200, info@valneva.com
Scientific contact	Clinical Operations, Valneva Austria GmbH, 0043 1206200, info@valneva.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2015
Global end of trial reached?	Yes
Global end of trial date	15 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the optimal dose and formulation of VLA84 in healthy adults aged ≥50 years

Protection of trial subjects:

Data Safety Monitoring Board (DSMB) was established to periodically review accruing safety information and if necessary, to determine during ad-hoc meetings whether study or individual subject stopping rules have been met.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 106
Country: Number of subjects enrolled	United States: 394
Worldwide total number of subjects	500
EEA total number of subjects	106

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)	250
From 65 to 84 years	247
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Study participants were recruited via sites' databases and/ or advertisements. Recruitment occurred at three study sites in Germany and seven sites in the US. A total of 509 subjects were recruited (thereof 9 were screening failures) during December 2014 till March 2015.

Pre-assignment

Screening details:

A total of 509 subjects were screened, thereof 9 were screening failures: 7 were screening failures (inclusion/ exclusion criteria), 1 withdrew consent prior, 1 subject: inability to obtain laboratory blood specimen.

Period 1

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

Blinding implementation details:

At each study site there was unblinded site personnel responsible for vaccine preparation; moreover there was an unblinded monitor who was solely responsible for drug accountability.
The study sponsor remained blinded until database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	VLA84 75 µg w/o Alum

Arm description:

At each vaccination day (Day 0, 7 and 28) two injections were administered: 0.75 mL VLA84 w/o Alum and 0.75 mL Placebo

Arm type	Experimental
Investigational medicinal product name	VLA84 w/o Alum
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

VLA 84 w/o Alum: C. difficile vaccine antigen is a recombinant fusion protein, formulated in a buffer without adjuvant. Depending on the assigned treatment group either 0.75 ml (treatment group VLA84 75 µg w/o Alum) or 2x 1.0 ml (treatment group VLA84 200 µg w/o Alum) are administered per vaccination day.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Phosphate Buffered Saline
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects assigned to the placebo group received 2x 1.0 ml placebo per vaccination day.

Arm title	VLA84 200 µg w/o Alum

Arm description:

At each vaccination day (Day 0, 7 and 28) 2x 1.0 mL VLA84 w/o Alum (i.e. a total of 2 ml) were administered.

Arm type	Experimental

Investigational medicinal product name	VLA84 w/o Alum
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

VLA 84 w/o Alum: C. difficile vaccine antigen is a recombinant fusion protein, formulated in a buffer without adjuvant. Depending on the assigned treatment group either 0.75 ml (treatment group VLA84 75 µg w/o Alum) or 2x 1.0 ml (treatment group VLA84 200 µg w/o Alum) are administered per vaccination day.

Arm title	VLA84 200 µg w/ Alum

Arm description:

At each vaccination day (Day 0, 7 and 28) 2x 1.0 mL VLA84 w/ Alum (i.e. a total of 2 ml) were administered.

Arm type	Experimental
Investigational medicinal product name	VLA84 w/ Alum
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

VLA 84 w/ Alum: C. difficile vaccine antigen is a recombinant fusion protein, formulated in a buffer and adjuvanted with Aluminium Hydroxide. 2x 1.0 ml (treatment group VLA84 200 µg w/ Alum) are administered per vaccination day.

Arm title	Placebo

Arm description:

At each vaccination day (Day 0, 7 and 28) 2x 1.0 mL placebo (i.e. a total of 2 ml) were administered.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Phosphate Buffered Saline
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects assigned to the placebo group received 2x 1.0 ml placebo per vaccination day.

Number of subjects in period 1	VLA84 75 µg w/o Alum	VLA84 200 µg w/o Alum	VLA84 200 µg w/ Alum
Started	148	152	152
Day 56	147	149	151
Completed	143	146	147
Not completed	5	6	5
Adverse event, serious fatal	1	-	-
Moved from study area	-	3	3
Consent withdrawn by subject	-	2	-
SUBJECT OUT OF TIME WINDOW AND UNCLEAR	1	-	-
PATIENT IS IN EXTENDED CARE FACILITY	-	-	1

Lost to follow-up	3	1	1

Number of subjects in period 1	Placebo
Started	48
Day 56	47
Completed	46
Not completed	2
Adverse event, serious fatal	-
Moved from study area	-
Consent withdrawn by subject	-
SUBJECT OUT OF TIME WINDOW AND UNCLEAR	-
PATIENT IS IN EXTENDED CARE FACILITY	-
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall study period

Reporting group description: -

Reporting group values	Overall study period	Total	
Number of subjects	500	500	
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
50 to < 65 years	250	250	
65 years and older	250	250	
Age continuous Units: years			
arithmetic mean	64		
standard deviation	± 9.13	-	
Gender categorical Units: Subjects			
Female	268	268	
Male	232	232	

End points

End points reporting groups

Reporting group title	VLA84 75 µg w/o Alum
Reporting group description:	
At each vaccination day (Day 0, 7 and 28) two injections were administered: 0.75 mL VLA84 w/o Alum and 0.75 mL Placebo	
Reporting group title	VLA84 200 µg w/o Alum
Reporting group description:	
At each vaccination day (Day 0, 7 and 28) 2x 1.0 mL VLA84 w/o Alum (i.e. a total of 2 ml) were administered.	
Reporting group title	VLA84 200 µg w/ Alum
Reporting group description:	
At each vaccination day (Day 0, 7 and 28) 2x 1.0 mL VLA84 w/ Alum (i.e. a total of 2 ml) were administered.	
Reporting group title	Placebo
Reporting group description:	
At each vaccination day (Day 0, 7 and 28) 2x 1.0 mL placebo (i.e. a total of 2 ml) were administered.	

Primary: Seroconversion Rate for IgG against both Toxin A and Toxin B on Day 56

End point title	Seroconversion Rate for IgG against both Toxin A and Toxin B on Day 56
End point description:	
Seroconversion Rate (SCR): defined as proportion of subjects achieving a ≥4-fold increase in antibody titer from Day 0; per-protocol population was primary analysis population (i.e., excluding subjects with major protocol deviations)	
End point type	Primary
End point timeframe:	
from Day 0 up to Day 56	

End point values	VLA84 75 µg w/o Alum	VLA84 200 µg w/o Alum	VLA84 200 µg w/ Alum	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	137	135	141	46
Units: proportion of subjects	98	112	84	0

Statistical analyses

Statistical analysis title	overall comparison of seroconversion rates (SCRs)
Statistical analysis description:	
The primary analysis compared the SCR against both Toxin A and Toxin B in the per-protocol (PP210) population between groups on Day 56, using a Cochran-Mantel-Haenszel (CMH) test stratified by age (50-64 vs. ≥ 65 years). Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was presented. As an overall test was produced before pair-wise comparisons were generated, no adjustment for multiple testing was performed.	
Comparison groups	VLA84 200 µg w/o Alum v VLA84 200 µg w/ Alum v VLA84 75 µg w/o Alum v Placebo

Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Inferential analysis;
Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was done. As an overall test was produced before pair-wise comparisons are generated, no adjustment for multiple testing was performed.

Statistical analysis title	comparison of SCR 75 w/o Alum vs. 200 w/o Alum

Statistical analysis description:

The primary analysis compared the SCR against both Toxin A and Toxin B in the per-protocol (PP210) population between groups on Day 56, using a Cochran-Mantel-Haenszel (CMH) test stratified by age (50-64 vs. ≥ 65 years). Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was presented. As an overall test was produced before pair-wise comparisons were generated, no adjustment for multiple testing was performed.

Comparison groups	VLA84 75 µg w/o Alum v VLA84 200 µg w/o Alum
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0261
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Inferential analysis;
Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was done. As an overall test was produced before pair-wise comparisons are generated, no adjustment for multiple testing was performed.

Statistical analysis title	comparison of SCR 75 w/o Alum vs. 200 w/ Alum

Statistical analysis description:

The primary analysis compared the SCR against both Toxin A and Toxin B in the per-protocol (PP210) population between groups on Day 56, using a Cochran-Mantel-Haenszel (CMH) test stratified by age (50-64 vs. ≥ 65 years). Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was presented. As an overall test was produced before pair-wise comparisons were generated, no adjustment for multiple testing was performed.

Comparison groups	VLA84 75 µg w/o Alum v VLA84 200 µg w/ Alum
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0364
Method	Cochran-Mantel-Haenszel

Notes:

[3] - Inferential analysis;
Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was done. As an overall test was produced before pair-wise comparisons are generated, no adjustment for multiple testing was performed.

Statistical analysis title	comparison of SCR 75 w/o Alum vs. placebo

Statistical analysis description:

The primary analysis compared the SCR against both Toxin A and Toxin B in the per-protocol (PP210) population between groups on Day 56, using a Cochran-Mantel-Haenszel (CMH) test stratified by age (50-64 vs. ≥ 65 years). Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was presented. As an overall test was produced before pair-wise comparisons were generated, no adjustment for multiple testing was performed.

Comparison groups	VLA84 75 µg w/o Alum v Placebo

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Inferential analysis;
Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was done. As an overall test was produced before pair-wise comparisons are generated, no adjustment for multiple testing was performed.

Statistical analysis title	comparison of SCR 200 w/o Alum vs. 200 w/ Alum

Statistical analysis description:

The primary analysis compared the SCR against both Toxin A and Toxin B in the per-protocol (PP210) population between groups on Day 56, using a Cochran-Mantel-Haenszel (CMH) test stratified by age (50-64 vs. ≥ 65 years). Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was presented. As an overall test was produced before pair-wise comparisons were generated, no adjustment for multiple testing was performed.

Comparison groups	VLA84 200 µg w/o Alum v VLA84 200 µg w/ Alum
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Notes:

[5] - Inferential analysis;
Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was done. As an overall test was produced before pair-wise comparisons are generated, no adjustment for multiple testing was performed.

Statistical analysis title	comparison of SCR 200 w/o Alum vs. placebo

Statistical analysis description:

The primary analysis compared the SCR against both Toxin A and Toxin B in the per-protocol (PP210) population between groups on Day 56, using a Cochran-Mantel-Haenszel (CMH) test stratified by age (50-64 vs. ≥ 65 years). Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was presented. As an overall test was produced before pair-wise comparisons were generated, no adjustment for multiple testing was performed.

Comparison groups	VLA84 200 µg w/o Alum v Placebo
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Notes:

[6] - Inferential analysis;
Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was done. As an overall test was produced before pair-wise comparisons are generated, no adjustment for multiple testing was performed.

Statistical analysis title	comparison of SCR 200 w/ Alum vs. placebo

Statistical analysis description:

The primary analysis compared the SCR against both Toxin A and Toxin B in the per-protocol (PP210) population between groups on Day 56, using a Cochran-Mantel-Haenszel (CMH) test stratified by age (50-64 vs. ≥ 65 years). Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was presented. As an overall test was produced before pair-wise comparisons were generated, no adjustment for multiple testing was performed.

Comparison groups	Placebo v VLA84 200 µg w/ Alum

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Notes:

[7] - Inferential analysis;
Only in presence of a significant overall effect, pair-wise comparisons between groups using CMH tests stratified by age was done. As an overall test was produced before pair-wise comparisons are generated, no adjustment for multiple testing was performed.

Secondary: Geometric Mean Titers (GMTs) for Toxin A- specific IgG antibodies (ELISA) on Day 56

End point title	Geometric Mean Titers (GMTs) for Toxin A- specific IgG antibodies (ELISA) on Day 56

End point description:

per-protocol population was primary analysis population (i.e., excluding subjects with major protocol deviations)

End point type	Secondary

End point timeframe:

at Day 56

End point values	VLA84 75 µg w/o Alum	VLA84 200 µg w/o Alum	VLA84 200 µg w/ Alum	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	137	135	141	46
Units: EU/ml				
geometric mean (confidence interval 95%)	2868.9 (2068.9 to 3978.1)	4328.5 (3160.5 to 5928.3)	4687.6 (3650.6 to 6019.3)	33.9 (28.4 to 40.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) for Toxin B- specific IgG antibodies (ELISA) on Day 56

End point title	Geometric Mean Titers (GMTs) for Toxin B- specific IgG antibodies (ELISA) on Day 56

End point description:

per-protocol population was primary analysis population (i.e., excluding subjects with major protocol deviations)

End point type	Secondary

End point timeframe:

on Day 56

End point values	VLA84 75 µg w/o Alum	VLA84 200 µg w/o Alum	VLA84 200 µg w/ Alum	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	137	135	141	46
Units: EU/ml				
geometric mean (confidence interval 95%)	2370.5 (1641.2 to 3423.8)	3336.5 (2398.9 to 4640.7)	1449.4 (1001.8 to 2097.2)	107.8 (77 to 151)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Event (AE) collection started at the time of first study vaccination. AEs were captured until the last study visit, i.e., Visit 8 (Day 210). Solicited local and systemic AEs were captured in a diary during 7 consecutive days after each vaccination

Adverse event reporting additional description:

In addition memory aids were used for documentation of AEs up to Visit 6 (Day 56). Diary and memory aid were returned to and reviewed with site staff at the next visit. AEs beyond D56 were captured via interview of study participants during study visits.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	VLA84 75 mcg w/o Alum

Reporting group description:

At each vaccination day (Day 0, 7 and 28) two injections were administered: 0.75 mL VLA84 w/o Alum and 0.75 mL Placebo

Reporting group title	VLA84 200 µg w/o Alum

Reporting group description:

At each vaccination day (Day 0, 7 and 28) 2x 1.0 mL VLA84 w/o Alum (i.e. a total of 2 ml) were administered.

Reporting group title	VLA84 200 µg w/ Alum

Reporting group description:

At each vaccination day (Day 0, 7 and 28) 2x 1.0 mL VLA84 w/ Alum (i.e. a total of 2 ml) were administered.

Reporting group title	Placebo

Reporting group description:

At each vaccination day (Day 0, 7 and 28) 2x 1.0 mL placebo (i.e. a total of 2 ml) were administered.

Serious adverse events	VLA84 75 mcg w/o Alum	VLA84 200 µg w/o Alum	VLA84 200 µg w/ Alum
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 148 (2.70%)	5 / 152 (3.29%)	3 / 152 (1.97%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 152 (0.00%)	0 / 152 (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
Invasive ductal breast carcinoma			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 152 (0.66%)	0 / 152 (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			
International normalised ratio increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 148 (0.68%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Incarcerated incisional hernia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 148 (0.68%)	0 / 152 (0.00%)	0 / 152 (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
Cardiac disorders			
Acute myocardial infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 148 (0.68%)	0 / 152 (0.00%)	0 / 152 (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
Cardiac failure congestive			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Inguinal hernia repair			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 152 (0.00%)	0 / 152 (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
Nervous system disorders			
Cerebrovascular accident			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 152 (0.66%)	0 / 152 (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
General disorders and administration site conditions			
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 152 (0.66%)	0 / 152 (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
Device dislocation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 148 (0.68%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 148 (0.68%)	0 / 152 (0.00%)	0 / 152 (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
Ileus			

subjects affected / exposed	1 / 148 (0.68%)	0 / 152 (0.00%)	0 / 152 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 152 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 152 (0.66%)	0 / 152 (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
Psychiatric disorders			
Suicidal ideation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 148 (0.68%)	0 / 152 (0.00%)	0 / 152 (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
Musculoskeletal and connective tissue disorders			
Spinal column stenosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Histoplasmosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 148 (0.68%)	0 / 152 (0.00%)	0 / 152 (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			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 152 (0.66%)	0 / 152 (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
Gangrene			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	2 / 48 (4.17%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
International normalised ratio increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Incarcerated incisional hernia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Inguinal hernia repair				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				

alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device dislocation				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spinal column stenosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Histoplasmosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gangrene			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 48 (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	VLA84 75 mcg w/o Alum	VLA84 200 µg w/o Alum	VLA84 200 µg w/ Alum
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 148 (50.68%)	94 / 152 (61.84%)	89 / 152 (58.55%)
Nervous system disorders			
Headache			
subjects affected / exposed	36 / 148 (24.32%)	31 / 152 (20.39%)	36 / 152 (23.68%)
occurrences (all)	49	52	49
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	33 / 148 (22.30%)	62 / 152 (40.79%)	60 / 152 (39.47%)
occurrences (all)	73	137	129
Fatigue			
subjects affected / exposed	25 / 148 (16.89%)	32 / 152 (21.05%)	23 / 152 (15.13%)
occurrences (all)	33	41	28
Influenza like illness			
subjects affected / exposed	17 / 148 (11.49%)	30 / 152 (19.74%)	21 / 152 (13.82%)
occurrences (all)	21	38	27
Injection site erythema			
subjects affected / exposed	13 / 148 (8.78%)	23 / 152 (15.13%)	20 / 152 (13.16%)
occurrences (all)	21	33	23
Injection site pruritus			
subjects affected / exposed	9 / 148 (6.08%)	18 / 152 (11.84%)	15 / 152 (9.87%)
occurrences (all)	12	23	17
Injection site swelling			
subjects affected / exposed	7 / 148 (4.73%)	14 / 152 (9.21%)	17 / 152 (11.18%)
occurrences (all)	8	20	20
Injection site induration			
subjects affected / exposed	6 / 148 (4.05%)	14 / 152 (9.21%)	12 / 152 (7.89%)
occurrences (all)	7	17	16
Pyrexia			
subjects affected / exposed	4 / 148 (2.70%)	9 / 152 (5.92%)	3 / 152 (1.97%)
occurrences (all)	4	10	4
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	16 / 148 (10.81%)	12 / 152 (7.89%)	14 / 152 (9.21%)
occurrences (all)	20	16	18
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 148 (6.08%)	8 / 152 (5.26%)	5 / 152 (3.29%)
occurrences (all)	9	10	5
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	17 / 148 (11.49%)	29 / 152 (19.08%)	25 / 152 (16.45%)
occurrences (all)	23	38	29
Infections and infestations			
Sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 148 (2.03%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences (all)	3	1	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 48 (47.92%)		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 48 (27.08%)		
occurrences (all)	17		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	21		
Fatigue			
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	9		
Influenza like illness			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	6		
Injection site erythema			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		

Injection site pruritus subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Injection site swelling subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 3		
Injection site induration subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 5		
Pyrexia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 10		
Diarrhoea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 3		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 11		
Infections and infestations Sinusitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported