Clinical trial results:
An Exploratory Safety and Immunogenicity Study of Human Papillomavirus (HPV16+) Immunotherapy VB10.16 in Women with High Grade Cervical Intraepithelial Neoplasia (HSIL; CIN 2/3)

Summary

EudraCT number	2014-005576-28
Trial protocol	DE
Global end of trial date	17 January 2019

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019
Summary attachment (see zip file)	VB C-01 CSR Synopsis (VB C-01_CSR Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	VB C-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02529930
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	VACCIBODY A.S.
Sponsor organisation address	Gaustadalléen 21, Oslo, Norway, 0349
Public contact	Irene Skjørestad, VACCIBODY A.S., Head of Quality Assurance/Clinical Program Director, 0047 22958193, ISkjorestad@vaccibody.com
Scientific contact	Dr Agnete Fredriksen, VACCIBODY A.S., President and Chief Scientific Officer, 0047 22958193, ABFredriksen@vaccibody.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	07 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 January 2019
Global end of trial reached?	Yes
Global end of trial date	17 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was:
- To assess the safety/tolerability of 3 mg VB10.16 immunotherapy in patients with HPV16+ Cervical Intraepithelial Neoplasia Grade 2/3 (CIN 2/3).

The secondary objectives of the trial were:
- To assess immunogenicity of 3 mg VB10.16 immunotherapy in patients with HPV16+ Cervical Intraepithelial Neoplasia Grade 2/3 (CIN 2/3).
- To make a preliminary assessment of efficacy of VB10.16 immunotherapy.

Protection of trial subjects:

As per attached synopsis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	34
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study that involved four participating sites in Germany.

Pre-assignment

Screening details:

This was an exploratory, open-label, multicenter study with two phases; a Dosing Phase and an Expansion Phase, in patients with histologically confirmed HPV16+ associated CIN 2/3 HSIL which assessed the safety/tolerability, immunogenicity and efficacy of VB10.16 immunotherapy.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label, single arm study. No blinding of the patients or investigators was necessary

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Three 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 21-25 (Visit 2) and 20-24 days after the date of the second vaccination (Visit 3).

Arm type	Experimental
Investigational medicinal product name	VB10.16
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Intramuscular use

Dosage and administration details:

VB10.16 is a naked DNA plasmid vaccine supplied as a sterile, ready to use solution at a concentration of 3 mg/mL in 1 mL glass vials. VB10.16 was administered using the PharmaJet® Stratis 0.5 mL needle-free injection system to deliver the plasmid intramuscularly in the area over the lateral deltoid muscle. The delivery volume was 0.5 mL per injection. Two injections were administered at each vaccination time point. The two injections were given in different arms.

Arm title	Cohort 2

Arm description:

Three 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 27-32 (Visit 2) and 54-60 days after the date of the second vaccination (Visit 3).

Arm type	Experimental
Investigational medicinal product name	VB10.16
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Intramuscular use

Dosage and administration details:

VB10.16 is a naked DNA plasmid vaccine supplied as a sterile, ready to use solution at a concentration of 3 mg/mL in 1 mL glass vials. VB10.16 was administered using the PharmaJet® Stratis 0.5 mL needle-free injection system to deliver the plasmid intramuscularly in the area over the lateral deltoid muscle. The delivery volume was 0.5 mL per injection. Two injections were administered at each vaccination time point. The two injections were given in different arms.

Arm title	Expansion Cohort

Arm description:

Four 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 21-25 (Visit 2), 20-24 days after the date of the second vaccination (Visit 3) and at Week 16 (Visit 4).

Arm type	Experimental
Investigational medicinal product name	VB10.16
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Intramuscular use

Dosage and administration details:

VB10.16 is a naked DNA plasmid vaccine supplied as a sterile, ready to use solution at a concentration of 3 mg/mL in 1 mL glass vials. VB10.16 was administered using the PharmaJet® Stratis 0.5 mL needle-free injection system to deliver the plasmid intramuscularly in the area over the lateral deltoid muscle. The delivery volume was 0.5 mL per injection. Two injections were administered at each vaccination time point. The two injections were given in different arms.

Number of subjects in period 1	Cohort 1	Cohort 2	Expansion Cohort
Started	8	8	18
Completed	8	8	17
Not completed	0	0	1
Retrospectively determined as HPV16 negative	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Three 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 21-25 (Visit 2) and 20-24 days after the date of the second vaccination (Visit 3).	
Reporting group title	Cohort 2
Reporting group description:	
Three 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 27-32 (Visit 2) and 54-60 days after the date of the second vaccination (Visit 3).	
Reporting group title	Expansion Cohort
Reporting group description:	
Four 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 21-25 (Visit 2), 20-24 days after the date of the second vaccination (Visit 3) and at Week 16 (Visit 4).	

Reporting group values	Cohort 1	Cohort 2	Expansion Cohort
Number of subjects	8	8	18
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	8	18
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	8	8	18
Male	0	0	0
Cervical Dysplasia Categorisation at Baseline Units: Subjects			
CIN 2	8	8	8
CIN 3	0	0	10
HPV16 Status Units: Subjects			
HPV16 present	8	8	17
HPV16 not present	0	0	1

Reporting group values	Total		
Number of subjects	34		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	34		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	34		
Male	0		
Cervical Dysplasia Categorisation at Baseline			
Units: Subjects			
CIN 2	24		
CIN 3	10		
HPV16 Status			
Units: Subjects			
HPV16 present	33		
HPV16 not present	1		

Subject analysis sets

Subject analysis set title	Safety Evaluable Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received any amount of VB10.16.	
Subject analysis set title	Efficacy Evaluable Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All evaluable patients with at least one post-baseline colposcopic assessment and positive COBAS® HPV test.	
Subject analysis set title	Immunogenicity Evaluable Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All evaluable patients with an immunologic assessment performed during the study.	

Reporting group values	Safety Evaluable Population	Efficacy Evaluable Population	Immunogenicity Evaluable Population
Number of subjects	34	33	33
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)	34	33	33

From 65-84 years	0	0	0
85 years and over	0	0	0

Gender categorical Units: Subjects			
Female	34	33	33
Male	0	0	0
Cervical Dysplasia Categorisation at Baseline Units: Subjects			
CIN 2	24	23	23
CIN 3	10	10	10
HPV16 Status Units: Subjects			
HPV16 present	33	33	33
HPV16 not present	1	0	0

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Three 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 21-25 (Visit 2) and 20-24 days after the date of the second vaccination (Visit 3).	
Reporting group title	Cohort 2
Reporting group description:	
Three 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 27-32 (Visit 2) and 54-60 days after the date of the second vaccination (Visit 3).	
Reporting group title	Expansion Cohort
Reporting group description:	
Four 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 21-25 (Visit 2), 20-24 days after the date of the second vaccination (Visit 3) and at Week 16 (Visit 4).	
Subject analysis set title	Safety Evaluable Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received any amount of VB10.16.	
Subject analysis set title	Efficacy Evaluable Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All evaluable patients with at least one post-baseline colposcopic assessment and positive COBAS® HPV test.	
Subject analysis set title	Immunogenicity Evaluable Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All evaluable patients with an immunologic assessment performed during the study.	

Primary: Safety

End point title	Safety[1]
End point description:	
Number of patients with adverse events, including any dose limiting toxicities, laboratory assessments and physical findings.	
End point type	Primary
End point timeframe:	
Safety data was collected from the date of informed consent until 30 days after the last administration of VB10.16. Potential late-emerging AEs considered related to study treatment were recorded during the extended follow-up period for up to 12 months.	

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: Safety parameters were analysed using descriptive statistics.

End point values	Cohort 1	Cohort 2	Expansion Cohort	Safety Evaluable Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	8	18	34
Units: Number of patients with events				
Any TEAEs	8	8	17	33
Any drug-related TEAEs	8	8	17	33
Any Grade 3, 4 or 5 TEAEs	1	0	1	2

Any Grade 3, 4 or 5 drug-related TEAEs	0	0	1	1
Any serious TEAEs	0	0	0	0
Any serious drug-related TEAEs	0	0	0	0
Any TEAEs leading to discontinuation	0	0	0	0
Any dose limiting toxicities	0	0	0	0
Any deaths due to TEAEs	0	0	0	0
Any late-emergent AEs	0	2	6	8
Any drug-related late-emergent AEs	0	1	2	3
Any Grade 3, 4 or 5 late-emergent AEs	0	1	0	1
Any Grade 3, 4 or 5 drug-related late-emergent AEs	0	0	0	0
Any serious late-emergent AEs	0	0	0	0
Any serious drug-related late-emergent AEs	0	0	0	0
Any late-emergent AEs leading to discontinuation	0	0	0	0
Any deaths due to late-emergent AEs	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of VB10.16

End point title	Immunogenicity of VB10.16

End point description:

The monitoring of immune response by means of:
- The percentage of patients with E6/E7 specific cellular immune response in the blood.

End point type	Secondary

End point timeframe:

Blood sampling for peripheral immune response in Cohorts 1 and 2 took place on Visit 1, Visit 1B, Visit 2A, Visit 3A, Visit 5 and Visit 6.
In the expansion cohort, sampling took place on Visit 1, Visit 3, Visit 4, Visit 5 and Visit 6.

End point values	Cohort 1	Cohort 2	Expansion Cohort	Immunogenicity Evaluable Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	7	17	31
Units: Percentage of patients				
Systemic T cell response against E6/E7 antigens	6	7	17	30
No systemic T cell response against E6/E7 antigens	1	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy - HPV16 Clearance

End point title	Efficacy - HPV16 Clearance

End point description:

HPV16 testing performed using the Cobas® HPV test. Summary results presented in the additional attachment.

End point type	Secondary

End point timeframe:

Patients were assessed for HPV16 clearance at Visit 4 (week 8), Visit 5 (Week 16), Visit 6 (Week 24), Visit 7 (Month 9) and Visit 8 (Month 12).

End point values	Cohort 1	Cohort 2	Expansion Cohort	Efficacy Evaluable Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	8	17	33
Units: Number of patients	8	8	17	33

Attachments (see zip file)	VB C-01_EudraCT Summary Attachment_HPV

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy - CIN Categorisation

End point title	Efficacy - CIN Categorisation

End point description:

Patients had colposcopy performed at the time points specified. Histological grading of CIN lesions was based on the pathological assessment of representative biopsies of all visible lesions. Summary results presented in the additional attachment.

End point type	Secondary

End point timeframe:

CIN assessment was performed at Visit 1 (baseline), Visit 4 (Week 8), Visit 5 (Week 16), Visit 6 (Week 24), Visit 7 (Month 9) and Visit 8 (Month 12).

End point values	Cohort 1	Cohort 2	Expansion Cohort	Efficacy Evaluable Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	8	17	33
Units: Number of patients	8	8	17	33

Attachments (see zip file)	VB C-01_EudraCT Summary Attachment_CIN

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy - Lesion Regression (Best Overall Responses)

End point title	Efficacy - Lesion Regression (Best Overall Responses)

End point description:

As part of the CIN regression assessment, a response assessment was performed by the investigator at Visits 4-8. This table shows a summary of the best responses based on the investigator's assessments during the study.

End point type	Secondary

End point timeframe:

Lesion regression assessment was performed at Visit 4 (Week 8), Visit 5 (Week 16), Visit 6 (Week 24), Visit 7 (Month 9) and Visit 8 (Month 12).

End point values	Cohort 1	Cohort 2	Expansion Cohort	Efficacy Evaluable Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	8	17	33
Units: Number of patients				
Complete response	1	1	2	4
Partial response	4	3	14	21
Stable disease	3	4	1	8

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety data was collected from the time of informed consent until 30 days after the last administration of VB10.16. Potential late-emerging AEs considered related to study treatment were recorded during the extended follow-up period for up to 12 months.

Adverse event reporting additional description:

Safety was assessed by means of physical examination, vital signs, performance status, laboratory evaluations (haematology and biochemistry), recording of concurrent illness/therapy and adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

Three 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 21-25 (Visit 2) and 20-24 days after the date of the second vaccination (Visit 3).

Reporting group title	Cohort 2

Reporting group description:

Three 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 27-32 (Visit 2) and 54-60 days after the date of the second vaccination (Visit 3).

Reporting group title	Expansion Cohort

Reporting group description:

Four 3 mg/mL VB10.16 immunotherapy vaccinations administered on Day 1 (Visit 1), Day 21-25 (Visit 2), 20-24 days after the date of the second vaccination (Visit 3) and at Week 16 (Visit 4).

Reporting group title	Safety Evaluable Population

Reporting group description:

All patients who received any amount of VB10.16.

Serious adverse events	Cohort 1	Cohort 2	Expansion Cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Safety Evaluable Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 34 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1	Cohort 2	Expansion Cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	8 / 8 (100.00%)	17 / 18 (94.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Hot flush			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Dental care			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Electrocauterisation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			

Injection site pain			
subjects affected / exposed	8 / 8 (100.00%)	3 / 8 (37.50%)	16 / 18 (88.89%)
occurrences (all)	17	8	51
Injection site erythema			
subjects affected / exposed	3 / 8 (37.50%)	2 / 8 (25.00%)	12 / 18 (66.67%)
occurrences (all)	5	4	28
Injection site hypersensitivity			
subjects affected / exposed	6 / 8 (75.00%)	1 / 8 (12.50%)	7 / 18 (38.89%)
occurrences (all)	11	2	14
Injection site hyperaesthesia			
subjects affected / exposed	3 / 8 (37.50%)	2 / 8 (25.00%)	8 / 18 (44.44%)
occurrences (all)	8	4	30
Injection site swelling			
subjects affected / exposed	3 / 8 (37.50%)	2 / 8 (25.00%)	6 / 18 (33.33%)
occurrences (all)	5	4	15
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	5 / 18 (27.78%)
occurrences (all)	1	0	9
Pain			
subjects affected / exposed	1 / 8 (12.50%)	4 / 8 (50.00%)	1 / 18 (5.56%)
occurrences (all)	1	6	1
Swelling			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	3 / 18 (16.67%)
occurrences (all)	1	3	3
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	4 / 18 (22.22%)
occurrences (all)	0	0	5
Injection site haematoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Injection site pruritus			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 18 (11.11%)
occurrences (all)	0	1	3
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	4

Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Administration site bruise			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Application site haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Feeling hot			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Injection site bruising			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Injection site discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Injection site haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Injection site induration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Local swelling			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			

Vaginal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	4
Dysmenorrhoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Menstruation delayed			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vaginal discharge			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Emotional distress			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Listless			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Mood swings			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nervousness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Thermal burn			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 8 (50.00%)	6 / 8 (75.00%)	8 / 18 (44.44%)
occurrences (all)	4	10	10
Hyperaesthesia			
subjects affected / exposed	2 / 8 (25.00%)	4 / 8 (50.00%)	7 / 18 (38.89%)
occurrences (all)	3	10	13
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Migraine			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Disturbance in attention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Sciatica			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	1 / 18 (5.56%)
occurrences (all)	2	3	1
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Abdominal pain lower			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 8 (25.00%)	4 / 8 (50.00%)	6 / 18 (33.33%)
occurrences (all)	3	8	9
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Night sweats			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Alopecia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Back pain			

subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	1 / 18 (5.56%)
occurrences (all)	0	4	1
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	0 / 18 (0.00%)
occurrences (all)	0	5	0
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Muscle tightness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Arthritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	5 / 18 (27.78%)
occurrences (all)	2	1	5
Bacterial vaginosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Gastrointestinal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Laryngitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Fungal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Non-serious adverse events	Safety Evaluable Population		

Total subjects affected by non-serious adverse events subjects affected / exposed	33 / 34 (97.06%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Anogenital warts subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Vascular disorders Haematoma subjects affected / exposed occurrences (all) Hot flush subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2 1 / 34 (2.94%) 1 1 / 34 (2.94%) 1		
Surgical and medical procedures Dental care subjects affected / exposed occurrences (all) Electrocauterisation subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1 1 / 34 (2.94%) 1		
Pregnancy, puerperium and perinatal conditions Abortion spontaneous subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
General disorders and administration site conditions Injection site pain subjects affected / exposed occurrences (all) Injection site erythema subjects affected / exposed occurrences (all) Injection site hypersensitivity	27 / 34 (79.41%) 76 17 / 34 (50.00%) 37		

subjects affected / exposed	14 / 34 (41.18%)			
occurrences (all)	27			
Injection site hyperaesthesia				
subjects affected / exposed	13 / 34 (38.24%)			
occurrences (all)	42			
Injection site swelling				
subjects affected / exposed	11 / 34 (32.35%)			
occurrences (all)	24			
Fatigue				
subjects affected / exposed	6 / 34 (17.65%)			
occurrences (all)	10			
Pain				
subjects affected / exposed	6 / 34 (17.65%)			
occurrences (all)	8			
Swelling				
subjects affected / exposed	6 / 34 (17.65%)			
occurrences (all)	7			
Influenza like illness				
subjects affected / exposed	4 / 34 (11.76%)			
occurrences (all)	5			
Injection site haematoma				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	2			
Injection site pruritus				
subjects affected / exposed	3 / 34 (8.82%)			
occurrences (all)	4			
Malaise				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	4			
Pyrexia				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	3			
Administration site bruise				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Application site haemorrhage				

subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Injection site bruising			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Injection site discomfort			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Injection site haemorrhage			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	3		
Injection site induration			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Local swelling			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	4		
Dysmenorrhoea			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Menstruation delayed			

subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Vaginal discharge			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Emotional distress			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Listless			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Nervousness			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	2		
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	 1 / 34 (2.94%) 1 1 / 34 (2.94%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Hyperaesthesia subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) Disturbance in attention subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Sciatica subjects affected / exposed occurrences (all)	 18 / 34 (52.94%) 24 13 / 34 (38.24%) 26 2 / 34 (5.88%) 2 2 / 34 (5.88%) 3 1 / 34 (2.94%) 1 1 / 34 (2.94%) 1 1 / 34 (2.94%) 1		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	 1 / 34 (2.94%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 1 / 34 (2.94%) 2		
Eye disorders			

Eye irritation subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 6		
Abdominal pain subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3		
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3		
Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Gastritis subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Skin and subcutaneous tissue disorders			

Erythema subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed occurrences (all) Night sweats subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all)	12 / 34 (35.29%) 20 2 / 34 (5.88%) 3 1 / 34 (2.94%) 2 1 / 34 (2.94%) 1 1 / 34 (2.94%) 3 1 / 34 (2.94%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1 1 / 34 (2.94%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity	3 / 34 (8.82%) 3 3 / 34 (8.82%) 5 2 / 34 (5.88%) 2		

subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	5		
Bone pain			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	2		
Muscle tightness			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Arthritis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	2		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 34 (20.59%)		
occurrences (all)	8		
Bacterial vaginosis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		

Laryngitis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2015	This amendment resulted in protocol version 4.0, dated 24 September 2015. The following changes were made: Wording changes requested by the regulatory agency were implemented. Urine pregnancy tests before each vaccination were introduced for all patients. The pre-screening period was increased from 4 to 6 weeks. Colposcopy and documentation of the size of the CIN lesions with digital photography had to be repeated in case it was performed more than 4 weeks prior to the first vaccination. The timing of visits was clarified further. Additional minor corrections (spelling mistakes, formatting) were made.
23 August 2016	This amendment resulted in protocol version 5.0, dated 23 August 2016. The following changes were made: Rationale was provided for the selection of the Cohort 1 dosing schedule for the Expansion Phase of the study. This decision by the Cohort Review Committee was based on the results of the interim analysis of the safety, immunogenicity and clinical outcome data from the 16 women enrolled in the parallel dosing schedules (Cohorts 1 and 2). Introduction of the requirement for documentation of disease status and potential late emergent adverse events during the extended follow up and implementation of additional Visits 7 and 8, at 9 and 12 months, respectively. Patients were required to attend the site for the extended follow up examinations. Pregnancy testing was made mandatory prior to each vaccination and during all follow up visits to ensure any unexpected pregnancies were brought to the attention of VACCIBODY A.S. and pregnancy outcomes documented accordingly. Additional minor corrections (spelling mistakes, formatting) were made.
09 March 2017	This amendment resulted in protocol version 6.0, dated 09 March 2017. The following changes were made: Addition of a fourth vaccination in the Expansion Phase of the study. This decision was based on the results of the safety, immunogenicity and clinical outcome data from the 16 women enrolled in the parallel dosing schedules (Cohorts 1 and 2) during the Dosing Phase. Introduction of a pregnancy test at Visit 5, before the fourth vaccination. Additional exploratory analysis of the potentially relevant immune markers was performed on the blood and tissue samples to gain a better understanding of the immune response after dose administration. Additional minor corrections (spelling mistakes, formatting) were made.
27 March 2018	This amendment resulted in protocol version 7.0, dated 27 March 2018. The amendment was submitted to inform about a change in the analyses arrangement. It made reference to a final CSR at Week 24 of the Expansion Phase of the study, with a follow up report including data from Visit 7 (Month 9) and Visit 8 (Month 12). However, this CSR was finalised after the full data set for all patients was available, after Visit 8 (Month 12). The amended protocol stated: 'An interim analysis was done in the Dosing Phase after 16 weeks and a final analysis done after 24 weeks of the Expansion Phase, which is included in this CSR. Following study completion after 12 months of the Expansion Phase, a CSR addendum with applicable data will be produced.'

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

6 patients underwent a conization procedure during the study. The conizations affected the efficacy and/or immunogenicity results in each cohort and are therefore, after conization, presented separately in the tables.

Notes: