



## 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:

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**Results analysis stage**

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|  |                 |
|--|-----------------|
| 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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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      |
| <b>Arm title</b>             | 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.

|                  |          |
|------------------|----------|
| <b>Arm title</b> | 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.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Expansion Cohort |
|------------------|------------------|

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**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.

| <b>Number of subjects in period 1</b>        | 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:<br>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:<br>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:<br>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<br>Units: Subjects                               |          |          |                  |
| In utero   | 0        | 0        | 0                |
| Preterm newborn infants<br>(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<br>Units: Subjects                            |          |          |                  |
| Female   | 8        | 8        | 18               |
| Male   | 0        | 0        | 0                |
| Cervical Dysplasia Categorisation at Baseline<br>Units: Subjects |          |          |                  |
| CIN 2  | 8        | 8        | 8                |
| CIN 3  | 0        | 0        | 10               |
| HPV16 Status<br>Units: Subjects                                  |          |          |                  |
| HPV16 present  | 8        | 8        | 17               |
| HPV16 not present  | 0        | 0        | 1                |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 34    |  |  |
| Age categorical<br>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<br>Units: Subjects                            |    |  |  |
| Female   | 34 |  |  |
| Male   | 0  |  |  |
| Cervical Dysplasia Categorisation at Baseline<br>Units: Subjects |    |  |  |
| CIN 2  | 24 |  |  |
| CIN 3  | 10 |  |  |
| HPV16 Status<br>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:<br>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:<br>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:<br>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<br>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<br>Units: Subjects                               |    |    |    |
| Female  | 34 | 33 | 33 |
| Male  | 0  | 0  | 0  |
| Cervical Dysplasia Categorisation at<br>Baseline<br>Units: Subjects |    |    |    |
| CIN 2   | 24 | 23 | 23 |
| CIN 3   | 10 | 10 | 10 |
| HPV16 Status<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>All evaluable patients with an immunologic assessment performed during the study.  |                                     |

### Primary: Safety

|   |                       |
|---|-----------------------|
| End point title   | Safety <sup>[1]</sup> |
| End point description:<br>Number of patients with adverse events, including any dose limiting toxicities, laboratory assessments and physical findings.   |                       |
| End point type  | Primary               |
| End point timeframe:<br>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_HP |
|----------------------------|---------------------------------------|

### 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                            |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | 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 %

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

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

|  |                     |                     |                      |
|--|---------------------|---------------------|----------------------|
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 1 / 18 (5.56%)<br>2  |
| Eye disorders<br>Eye irritation<br>subjects affected / exposed<br>occurrences (all)        | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 18 (0.00%)<br>0  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)   | 2 / 8 (25.00%)<br>2 | 1 / 8 (12.50%)<br>3 | 1 / 18 (5.56%)<br>1  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 8 (0.00%)<br>0  | 2 / 8 (25.00%)<br>2 | 1 / 18 (5.56%)<br>1  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 2 / 18 (11.11%)<br>2 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 2 / 18 (11.11%)<br>3 |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 18 (0.00%)<br>0  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 8 (12.50%)<br>1 | 0 / 8 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 8 (12.50%)<br>1 | 0 / 8 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)       | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 18 (0.00%)<br>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<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1 |
| Influenza<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1 | 0 / 8 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 |
| Laryngitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 18 (0.00%)<br>0 |
| Paronychia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 8 (12.50%)<br>1 | 0 / 8 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1 |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 18 (0.00%)<br>0 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1 | 0 / 8 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 |
| Vulvovaginal mycotic infection<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1 |
| Fungal infection<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1 |
| Tonsillitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 18 (0.00%)<br>0 |
| Metabolism and nutrition disorders<br>Type 2 diabetes mellitus<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1 |

|                                   |                                |  |  |
|-----------------------------------|--------------------------------|--|--|
| <b>Non-serious adverse events</b> | Safety Evaluable<br>Population |  |  |
|-----------------------------------|--------------------------------|--|--|

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

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

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

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

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

|                                |                 |  |  |
|--------------------------------|-----------------|--|--|
| 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 | <p>This amendment resulted in protocol version 4.0, dated 24 September 2015.</p> <p>The following changes were made:</p> <p>Wording changes requested by the regulatory agency were implemented.</p> <p>Urine pregnancy tests before each vaccination were introduced for all patients.</p> <p>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.</p> <p>The timing of visits was clarified further.</p> <p>Additional minor corrections (spelling mistakes, formatting) were made.</p>   |
| 23 August 2016    | <p>This amendment resulted in protocol version 5.0, dated 23 August 2016.</p> <p>The following changes were made:</p> <p>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).</p> <p>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.</p> <p>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.</p> <p>Additional minor corrections (spelling mistakes, formatting) were made.</p> |
| 09 March 2017     | <p>This amendment resulted in protocol version 6.0, dated 09 March 2017.</p> <p>The following changes were made:</p> <p>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.</p> <p>Introduction of a pregnancy test at Visit 5, before the fourth vaccination.</p> <p>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.</p> <p>Additional minor corrections (spelling mistakes, formatting) were made.</p>  |
| 27 March 2018     | <p>This amendment resulted in protocol version 7.0, dated 27 March 2018.</p> <p>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).</p> <p>The amended protocol stated:</p> <p>'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.'</p>  |

Notes:



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## **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: