



## Clinical trial results:

### Phase II Placebo-Controlled Study of VGX-3100, (HPV-16 E6/E7, HPV-18 E6/E7 DNA Vaccine) Delivered IM Followed by Electroporation (EP) with CELLECTRA™-5P for the Treatment of Biopsy-Proven CIN2/3 or CIN3 with Documented HPV-16 or 18

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-001334-33 |
| Trial protocol           | EE             |
| Global end of trial date | 17 April 2015  |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 26 July 2017 |
| First version publication date | 26 July 2017 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | HPV-003 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01304524 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                       |
|------------------------------|-------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Inovio Pharmaceuticals, Inc                                                                           |
| Sponsor organisation address | 660 W Germantown Pike, Suite 110, Plymouth Meeting, PA, United States, 19462                          |
| Public contact               | Inovio Pharmaceuticals, Inc, Inovio Pharmaceuticals, Inc, +1 267-440-4200, clinical.trials@inovio.com |
| Scientific contact           | Inovio Pharmaceuticals, Inc, Inovio Pharmaceuticals, Inc, +1 267-440-4200, clinical.trials@inovio.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                       | 17 April 2015 |
| Is this the analysis of the primary completion data? | No            |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 17 April 2015 |
| Was the trial ended prematurely? | No            |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the histologic response to three 6 milligram (mg) doses of VGX-3100 administered by intramuscular (IM) injection in combination with electroporation (EP) delivered by the CELLECTRA™-5P constant current device in adult females with biopsy-proven human papillomavirus (HPV)-16 or 18 associated cervical intraepithelial neoplasia (CIN) grade 2/3 or CIN 3.

Protection of trial subjects:

After the study was fully explained, written informed consent was obtained from the subject prior to study participation.

Background therapy: -

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 13 September 2011 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety, Efficacy  |
| Long term follow-up duration                              | 12 Months         |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 109 |
| Country: Number of subjects enrolled | Canada: 5          |
| Country: Number of subjects enrolled | Australia: 3       |
| Country: Number of subjects enrolled | Georgia: 1         |
| Country: Number of subjects enrolled | India: 6           |
| Country: Number of subjects enrolled | Puerto Rico: 5     |
| Country: Number of subjects enrolled | South Africa: 12   |
| Country: Number of subjects enrolled | Estonia: 26        |
| Worldwide total number of subjects   | 167                |
| EEA total number of subjects         | 26                 |

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)                     | 167 |
| From 65 to 84 years                      | 0   |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Female subjects, age 18-55 years with histologically confirmed HPV-16 or HPV-18-associated CIN 2/3 or CIN 3 from tissue collected less than 10 weeks prior to first study treatment without evidence of invasive cancer in any specimen, were recruited into the study.

### Pre-assignment

Screening details:

Randomisation was stratified by age (<25 years versus ≥25 years) and CIN2 versus CIN3 (3:1 = VGX-3100:placebo). Subject disposition is based on the safety population and includes all subjects, who received at least 1 dose (investigational product [IP] and electroporation [EP]).

### Period 1

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

### Arms

|                              |               |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes           |
| <b>Arm title</b>             | VGX-3100 + EP |

Arm description:

Adult women with biopsy-proven HPV-16 or 18 associated with CIN 2/3 or CIN 3 were administered VGX-3100 deoxyribonucleic acid (DNA) vaccine followed by EP with CELLECTRA™-5P on Day 0, Week 4 and Week 12.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | VGX-3100               |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intramuscular use      |

Dosage and administration details:

Six mg, 1 milliliter (mL) doses of VGX-3100 DNA vaccine, including plasmids targeting E6 and E7 proteins of both HPV subtypes 16 and 18, were injected IM followed by EP with CELLECTRA™-5P, a constant current device which delivers a small electric charge to aid in the delivery of DNA vaccines, on Day 0, Week 4 and Week 12.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Placebo + EP |
|------------------|--------------|

Arm description:

Adult women with biopsy-proven HPV 16 or 18 associated with CIN 2/3 or CIN 3 were administered matching placebo to VGX-3100 followed by EP with CELLECTRA™-5P on Day 0, Week 4 and Week 12.

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

Dosage and administration details:

A 1 mL dose of sterile water as matching placebo to VGX-3100 DNA vaccine was injected IM followed by EP with CELLECTRA™-5P, a constant current device which delivers a small electric charge, on Day 0, Week 4 and Week 12.

| <b>Number of subjects in period 1</b>              | VGX-3100 + EP | Placebo + EP |
|----------------------------------------------------|---------------|--------------|
| Started                                            | 125           | 42           |
| Completed                                          | 102           | 36           |
| Not completed                                      | 23            | 6            |
| Adverse Event                                      | 3             | 2            |
| Decision by investigator                           | 1             | -            |
| Decision by subject (not related to adverse event) | 3             | 2            |
| Pregnancy                                          | -             | 1            |
| Other reason                                       | 2             | -            |
| Lost to follow-up                                  | 14            | 1            |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | VGX-3100 + EP |
|-----------------------|---------------|

Reporting group description:

Adult women with biopsy-proven HPV-16 or 18 associated with CIN 2/3 or CIN 3 were administered VGX-3100 deoxyribonucleic acid (DNA) vaccine followed by EP with CELLECTRA™-5P on Day 0, Week 4 and Week 12.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Placebo + EP |
|-----------------------|--------------|

Reporting group description:

Adult women with biopsy-proven HPV 16 or 18 associated with CIN 2/3 or CIN 3 were administered matching placebo to VGX-3100 followed by EP with CELLECTRA™-5P on Day 0, Week 4 and Week 12.

| Reporting group values | VGX-3100 + EP | Placebo + EP | Total |
|------------------------|---------------|--------------|-------|
| Number of subjects     | 125           | 42           | 167   |
| Age categorical        |               |              |       |
| Units: Subjects        |               |              |       |
| Adults (18-64 years)   | 125           | 42           | 167   |
| Age continuous         |               |              |       |
| Units: years           |               |              |       |
| arithmetic mean        | 29.4          | 31.6         |       |
| standard deviation     | ± 6.39        | ± 9.34       | -     |
| Gender categorical     |               |              |       |
| Units: Subjects        |               |              |       |
| Female                 | 125           | 42           | 167   |
| Male                   | 0             | 0            | 0     |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                             |               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Reporting group title                                                                                                                                                                                                                       | VGX-3100 + EP |
| Reporting group description:<br>Adult women with biopsy-proven HPV-16 or 18 associated with CIN 2/3 or CIN 3 were administered VGX-3100 deoxyribonucleic acid (DNA) vaccine followed by EP with CELLECTRA™-5P on Day 0, Week 4 and Week 12. |               |
| Reporting group title                                                                                                                                                                                                                       | Placebo + EP  |
| Reporting group description:<br>Adult women with biopsy-proven HPV 16 or 18 associated with CIN 2/3 or CIN 3 were administered matching placebo to VGX-3100 followed by EP with CELLECTRA™-5P on Day 0, Week 4 and Week 12.                 |               |

### Primary: Efficacy: Number of Subjects with Histopathological Regression of Cervical Lesions to CIN 1 or Less in the Per Protocol Population

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Efficacy: Number of Subjects with Histopathological Regression of Cervical Lesions to CIN 1 or Less in the Per Protocol Population |
| End point description:<br>The number of subjects with histopathologically confirmed CIN2/3 or CIN 3 associated with HPV-16 or HPV-18 whose cervical lesions regressed to CIN 1 or less at the Week 36 visit. Non-regressors were defined as subjects with a tissue diagnosis of CIN2/3 at Week 36. Subjects from whom tissue (e.g. biopsy) was obtained before Week 36 based on suspicion of disease progression were also classified as non-regressors, regardless of histological diagnosis. The Per Protocol (PP) population included all subjects who received 3 doses (IP and EP), underwent a biopsy/surgical excision starting from 14 days prior to Week 36 through the end of the study with no protocol violations, unless an earlier biopsy/surgical excision was performed due to disease progression. |                                                                                                                                    |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Primary                                                                                                                            |
| End point timeframe:<br>Week 36                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                    |

| End point values            | VGX-3100 + EP   | Placebo + EP    |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 105             | 36              |  |  |
| Units: number of subjects   |                 |                 |  |  |
| number (not applicable)     | 51              | 11              |  |  |

### Statistical analyses

|                                                                                                                                           |                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Statistical analysis title                                                                                                                | VGX-3100 + EP versus Placebo + EP |
| Statistical analysis description:<br>The primary hypothesis was that VGX-3100 + EP is superior to placebo + EP for the entire population. |                                   |
| Comparison groups                                                                                                                         | VGX-3100 + EP v Placebo + EP      |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 141                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.043                     |
| Method                                  | Mehrotra's test             |
| Parameter estimate                      | Percentage point difference |
| Point estimate                          | 18.2                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.6                         |
| upper limit                             | 35.8                        |

### **Primary: Efficacy: Number of Subjects with Histopathological Regression of Cervical Lesions to CIN 1 or Less in the Modified Intention-to-Treat Population**

|                 |                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Efficacy: Number of Subjects with Histopathological Regression of Cervical Lesions to CIN 1 or Less in the Modified Intention-to-Treat Population |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

The number of subjects with histopathologically confirmed CIN2/3 or CIN 3 associated with HPV-16 or HPV-18 whose cervical lesions regressed to CIN 1 or less at the Week 36 visit. Non-regressors were defined as subjects with a tissue diagnosis of CIN2/3 at Week 36. Subjects from whom tissue (e.g. biopsy) was obtained before Week 36 based on suspicion of disease progression were also classified as non-regressors, regardless of histological diagnosis. The modified Intention-to-Treat (ITT) population included all subjects who received at least 1 dose (IP and EP) and underwent a biopsy/surgical excision starting from 14 days prior to Week 36 through the end of the study, unless an earlier biopsy/surgical excision was performed due to disease progression.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

#### End point timeframe:

Week 36

| <b>End point values</b>     | VGX-3100 + EP   | Placebo + EP    |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 114             | 40              |  |  |
| Units: number of subjects   |                 |                 |  |  |
| number (not applicable)     | 55              | 12              |  |  |

### **Statistical analyses**

|                                                                                                      |                                   |
|------------------------------------------------------------------------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>                                                                    | VGX-3100 + EP versus Placebo + EP |
| Statistical analysis description:                                                                    |                                   |
| The primary hypothesis was that VGX-3100 + EP is superior to placebo + EP for the entire population. |                                   |
| Comparison groups                                                                                    | Placebo + EP v VGX-3100 + EP      |



|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 154                         |
| Analysis specification                  | Post-hoc                    |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.034                     |
| Method                                  | Mehrotra's test             |
| Parameter estimate                      | Percentage point difference |
| Point estimate                          | 17.8                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.3                         |
| upper limit                             | 34.4                        |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline to end of follow-up at Week 88.

Adverse event reporting additional description:

The safety population included all subjects who received at least 1 dose (IP or EP).

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | VGX-3100 + EP |
|-----------------------|---------------|

Reporting group description:

Adult women with biopsy-proven HPV-16 or 18 associated with CIN 2/3 or CIN 3 were administered VGX-3100 deoxyribonucleic acid (DNA) vaccine followed by electroporation with CELLECTRA™-5P on Day 0, Week 4 and Week 12.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Placebo + EP |
|-----------------------|--------------|

Reporting group description:

Adult women with biopsy-proven HPV 16 or 18 associated with CIN 2/3 or CIN 3 were administered matching placebo to VGX-3100 followed by electroporation with CELLECTRA™-5P on Day 0, Week 4 and Week 12.

| Serious adverse events                                              | VGX-3100 + EP   | Placebo + EP   |  |
|---------------------------------------------------------------------|-----------------|----------------|--|
| Total subjects affected by serious adverse events                   |                 |                |  |
| subjects affected / exposed                                         | 7 / 125 (5.60%) | 4 / 42 (9.52%) |  |
| number of deaths (all causes)                                       | 0               | 0              |  |
| number of deaths resulting from adverse events                      | 0               | 0              |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                |  |
| Squamous cell carcinoma of the cervix                               |                 |                |  |
| subjects affected / exposed                                         | 1 / 125 (0.80%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 1          |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          |  |
| Cervix carcinoma stage 0                                            |                 |                |  |
| subjects affected / exposed                                         | 2 / 125 (1.60%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all                     | 0 / 2           | 0 / 1          |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          |  |
| Breast cancer stage I                                               |                 |                |  |

|                                                 |                 |                |  |
|-------------------------------------------------|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 125 (0.80%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Adenosquamous carcinoma of the cervix           |                 |                |  |
| subjects affected / exposed                     | 1 / 125 (0.80%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                 |                |  |
| Post procedural bleeding                        |                 |                |  |
| subjects affected / exposed                     | 1 / 125 (0.80%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Nervous system disorders                        |                 |                |  |
| Tension headache                                |                 |                |  |
| subjects affected / exposed                     | 0 / 125 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Reproductive system and breast disorders        |                 |                |  |
| Vaginal haemorrhage                             |                 |                |  |
| subjects affected / exposed                     | 0 / 125 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                 |                |  |
| Pulmonary embolism                              |                 |                |  |
| subjects affected / exposed                     | 1 / 125 (0.80%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | <b>VGX-3100 + EP</b>   | <b>Placebo + EP</b> |  |
|-------------------------------------------------------|------------------------|---------------------|--|
| Total subjects affected by non-serious adverse events |                        |                     |  |
| subjects affected / exposed                           | 125 / 125<br>(100.00%) | 42 / 42 (100.00%)   |  |
| Investigations                                        |                        |                     |  |
| Blood pressure increased                              |                        |                     |  |
| subjects affected / exposed                           | 4 / 125 (3.20%)        | 5 / 42 (11.90%)     |  |
| occurrences (all)                                     | 9                      | 5                   |  |
| Nervous system disorders                              |                        |                     |  |
| Headache                                              |                        |                     |  |
| subjects affected / exposed                           | 53 / 125 (42.40%)      | 24 / 42 (57.14%)    |  |
| occurrences (all)                                     | 142                    | 56                  |  |
| Migraine                                              |                        |                     |  |
| subjects affected / exposed                           | 9 / 125 (7.20%)        | 1 / 42 (2.38%)      |  |
| occurrences (all)                                     | 11                     | 1                   |  |
| General disorders and administration site conditions  |                        |                     |  |
| Fatigue                                               |                        |                     |  |
| subjects affected / exposed                           | 69 / 125 (55.20%)      | 20 / 42 (47.62%)    |  |
| occurrences (all)                                     | 150                    | 56                  |  |
| Injection site bruising                               |                        |                     |  |
| subjects affected / exposed                           | 16 / 125 (12.80%)      | 3 / 42 (7.14%)      |  |
| occurrences (all)                                     | 25                     | 3                   |  |
| Injection site erythema                               |                        |                     |  |
| subjects affected / exposed                           | 98 / 125 (78.40%)      | 24 / 42 (57.14%)    |  |
| occurrences (all)                                     | 212                    | 49                  |  |
| Injection site haematoma                              |                        |                     |  |
| subjects affected / exposed                           | 1 / 125 (0.80%)        | 3 / 42 (7.14%)      |  |
| occurrences (all)                                     | 1                      | 4                   |  |
| Injection site joint pain                             |                        |                     |  |
| subjects affected / exposed                           | 3 / 125 (2.40%)        | 3 / 42 (7.14%)      |  |
| occurrences (all)                                     | 7                      | 4                   |  |
| Injection site pain                                   |                        |                     |  |
| subjects affected / exposed                           | 119 / 125 (95.20%)     | 40 / 42 (95.24%)    |  |
| occurrences (all)                                     | 593                    | 196                 |  |
| Injection site pruritus                               |                        |                     |  |
| subjects affected / exposed                           | 12 / 125 (9.60%)       | 8 / 42 (19.05%)     |  |
| occurrences (all)                                     | 18                     | 11                  |  |

|                                                                                                                   |                          |                        |  |
|-------------------------------------------------------------------------------------------------------------------|--------------------------|------------------------|--|
| Injection site swelling<br>subjects affected / exposed<br>occurrences (all)                                       | 63 / 125 (50.40%)<br>139 | 14 / 42 (33.33%)<br>27 |  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)                                                       | 40 / 125 (32.00%)<br>71  | 11 / 42 (26.19%)<br>25 |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                                                       | 7 / 125 (5.60%)<br>10    | 0 / 42 (0.00%)<br>0    |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 125 (0.80%)<br>1     | 3 / 42 (7.14%)<br>3    |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                        | 32 / 125 (25.60%)<br>52  | 11 / 42 (26.19%)<br>23 |  |
| Reproductive system and breast disorders<br>Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all)     | 8 / 125 (6.40%)<br>13    | 2 / 42 (4.76%)<br>3    |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                              | 9 / 125 (7.20%)<br>9     | 0 / 42 (0.00%)<br>0    |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 16 / 125 (12.80%)<br>24  | 11 / 42 (26.19%)<br>15 |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                                                       | 49 / 125 (39.20%)<br>109 | 15 / 42 (35.71%)<br>26 |  |
| Infections and infestations<br>Influenza<br>subjects affected / exposed<br>occurrences (all)                      | 11 / 125 (8.80%)<br>20   | 3 / 42 (7.14%)<br>3    |  |
| Nasopharyngitis                                                                                                   |                          |                        |  |

|                                |                   |                 |  |
|--------------------------------|-------------------|-----------------|--|
| subjects affected / exposed    | 13 / 125 (10.40%) | 5 / 42 (11.90%) |  |
| occurrences (all)              | 19                | 5               |  |
| Sinusitis                      |                   |                 |  |
| subjects affected / exposed    | 12 / 125 (9.60%)  | 0 / 42 (0.00%)  |  |
| occurrences (all)              | 14                | 0               |  |
| Urinary tract infection        |                   |                 |  |
| subjects affected / exposed    | 13 / 125 (10.40%) | 1 / 42 (2.38%)  |  |
| occurrences (all)              | 16                | 1               |  |
| Vaginal infection              |                   |                 |  |
| subjects affected / exposed    | 8 / 125 (6.40%)   | 0 / 42 (0.00%)  |  |
| occurrences (all)              | 8                 | 0               |  |
| Vaginitis bacterial            |                   |                 |  |
| subjects affected / exposed    | 7 / 125 (5.60%)   | 1 / 42 (2.38%)  |  |
| occurrences (all)              | 8                 | 1               |  |
| Vulvovaginal candidiasis       |                   |                 |  |
| subjects affected / exposed    | 8 / 125 (6.40%)   | 0 / 42 (0.00%)  |  |
| occurrences (all)              | 12                | 0               |  |
| Vulvovaginal mycotic infection |                   |                 |  |
| subjects affected / exposed    | 4 / 125 (3.20%)   | 3 / 42 (7.14%)  |  |
| occurrences (all)              | 4                 | 4               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 March 2011     | Protocol version 1.1: The inclusion and exclusion criteria were clarified to include a satisfactory colposcopy and no evidence of invasive cancer in any specimen and exclude an unsatisfactory colposcopy and an endocervical curettage (ECC) specimen that identified endocervical CIN, that was not directly visualized. The cervical immunology and virologic samples to be collected in the study were clarified. The collection of pre-dose blood immunology samples for the exploratory endpoints was amended to include whole blood and serum samples at screening. A process for the supplementation of study subjects to include additional subjects to be randomized if more than 10 subjects received less than three vaccinations or underwent definitive therapy prior to Week 24 to maintain a per protocol sample size of at least 138 subjects was added. Further clarification was provided regarding the discontinuation and withdrawal of study subjects. Additional information regarding the assessment of injection site reactions to include the use of the "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (Sept 2007) for grading injection site reactions was added. The reporting period for unsolicited adverse events (AEs) was clarified to include the period following signing of the informed consent to study discharge and for solicited AEs to include the period following administration of study treatment through 4 weeks following each injection of VGX-3100 + EP. |
| 16 September 2011 | Protocol version 1.2: Clarified inclusion criteria to include voluntary signing of the informed consent form. Changed the inclusion criteria from "18-50" to "18-55" years of age. Removed the exclusion criterion about receiving any HPV vaccine at any time in the past. Updated temperature storage condition and label for VGX-3100. Added pregnancy testing prior to any colposcopy and surgical excision. Clarified instructions for subjects who became pregnant during the study. Clarified qualifications for site staff who were to dispense and administer vaccinations during the study. Clarified wording regarding subjects eligible for screening in the study. Updated investigational product information to include storage, handling and accounting of Placebo.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 19 December 2012  | Protocol version 1.3: Updated list of regions where the trial was being conducted. Eliminated optional collection of endocervical brush specimens. Eliminated collection of blood samples at Weeks 6, 36, 62 and collection of cervical samples at Week 6. Specified instructions to permit subjects with a cytological diagnosis of high grade squamous intraepithelial lesion (HGSIL) to undergo biopsy to determine CIN status after approval from the Sponsor's medical monitor on a case by case basis. Added optional collection of unstained slides or tissue at entry and Week 36 for immunohistochemical analysis. Extended screening period between entry biopsy and first treatment with vaccine/placebo to 10 weeks to allow adequate time to process pathology samples. Added the option to perform Week 2 and 6 study procedures via telephone contact to reduce visit burden on participants. A follow-up clinic visit was at the discretion of the study staff based on the need for further evaluation of any reported events. Added an Exploratory Objective to measure durability of immune responses. Added detail regarding the Data and Safety Monitoring Board (DSMB) reporting of primary aggregate treatment-specific results to Sponsor. Clarified rules for subject inclusion or exclusion from the primary per-protocol analysis. Corrected the Supplementation of Study Subjects section for subjects, who underwent definitive therapy prior to Week 36 and not Week 24.                                                                                                      |

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| 18 December 2013 | Protocol version 1.4: The protocol was amended to unblind when all subjects, who had not discontinued, completed their Week 40 Visit. This allowed the Sponsor to have a complete unblinded dataset with respect to the primary Week 36 Visit endpoint on which to make decisions regarding the VGX-3100 program, while awaiting outstanding secondary data through the final Week 88 Visit. Long-term follow up data continued to be collected on all subjects with remaining visits through the final Week 88 Visit post-unblinding, and all data were analysed accordingly in the final full Clinical Study Report. Subjects and study site personnel remained blinded to individual treatment assignment until after all subjects, who had not discontinued, completed their Week 88 visit. Access to this unblinded dataset replaced the DSMB's communication of unblinded primary results at Week 36 to the Sponsor. |
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported