



Clinical trial results:

REVEAL 2: A Prospective, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation with CELLECTRA™ 5PSP for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Cervix

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2018-004114-17 |
| Trial protocol | GB LT EE ES PL FI IT |
| Global end of trial date | 15 September 2022 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 27 September 2023 |
| First version publication date | 27 September 2023 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | HPV-303 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03721978 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Inovio Pharmaceuticals, Inc. |
| Sponsor organisation address | 660 W. Germantown Pike, Suite 110, Plymouth Meeting, United States, PA 19462 |
| Public contact | Clinical Development, Inovio Pharmaceuticals, Inc., +1 267-440-4200, HPV303ClinicalTeam@inovio.com |
| Scientific contact | Clinical Development, Inovio Pharmaceuticals, Inc., +1 267-440-4200, HPV303ClinicalTeam@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 | 16 August 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 September 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 September 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Among baseline biomarker-positive women determine the efficacy of VGX-3100 compared with placebo with respect to combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18

Protection of trial subjects:

This protocol was conducted in accordance with the applicable GCP regulations and guidelines and when applicable, in compliance with the regulations on electronic records and electronic signature. Subjects were not required to follow special instructions specific to the investigational product (IP) used in this clinical trial as the IP was handled and administered to subjects by the clinical trial personnel at the clinical trial site. Subjects were provided with investigator emergency contact information and advised to report all AEs. Written informed consent was to be obtained from each subject prior to enrollment into the clinical trial, and/or from the subject's legally authorized representative.

Background therapy:

Topical anesthetic (e.g., eutectic mixture of local anesthetics [EMLA] or equivalent) may have been offered to subjects to prevent significant discomfort from the treatment procedure; subjects may have been offered a mild sedative (e.g., 0.5 to 1 mg lorazepam or equivalent 1 hour prior to treatment) for anxiety related to the treatment procedure and were not to be allowed to operate a motor vehicle for 3 to 4 hours after receiving medication; subjects may have been offered an analgesic (e.g., ibuprofen or ketorolac) after injection/EP; subjects who were allergic to or had contraindications to listed concomitant medications may have been offered a suitable alternative; all concomitant medications have been added to eCRF respectively.

Evidence for comparator:

This was a placebo-controlled study.

| | |
|---|------------------|
| Actual start date of recruitment | 28 February 2019 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 1 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Argentina: 5 |
| Country: Number of subjects enrolled | Brazil: 24 |
| Country: Number of subjects enrolled | South Africa: 12 |
| Country: Number of subjects enrolled | United States: 41 |
| Country: Number of subjects enrolled | Spain: 20 |
| Country: Number of subjects enrolled | Estonia: 51 |
| Country: Number of subjects enrolled | Finland: 5 |

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Lithuania: 45 |
| Worldwide total number of subjects | 203 |
| EEA total number of subjects | 121 |

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) | 203 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects meeting all the inclusion criteria and none of the exclusion criteria were entered into the clinical trial. Eligible subjects were randomly assigned to receive either 6 mg VGX-3100 or placebo (ratio 2:1) IM followed by Electroporation (EP).

Pre-assignment

Screening details:

All screening evaluations were to be completed within 10 weeks prior to the first dose of clinical trial treatment (Day 0), except for the safety laboratory assessments, which were to be performed within 60 days prior to Day 0.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Treatment 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 |

Blinding implementation details:

This clinical trial was double-blinded with blinding maintained throughout the clinical trial by use of identical packaging for both the active product VGX-3100 and the placebo. There was no difference in appearance for both the active product and the placebo.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------------|
| Arm title | VGX-3100 + EP |
|------------------|---------------|

Arm description:

Eligible subjects received three (3) 6-mg doses of VGX-3100 refrigerated formulation IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device.

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

Dosage and administration details:

Eligible subjects received three (3) 6-mg doses (in 1 mL) of VGX-3100 refrigerated formulation.

| | |
|------------------|--------------|
| Arm title | Placebo + EP |
|------------------|--------------|

Arm description:

Eligible subjects received three (3) doses Placebo refrigerated formulation IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device.

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

Dosage and administration details:

Eligible subjects received three (3) doses Placebo (in 1 mL) of VGX-3100 refrigerated formulation.

| Number of subjects in period 1 | VGX-3100 + EP | Placebo + EP |
|---------------------------------------|---------------|--------------|
| Started | 134 | 69 |
| Completed | 121 | 64 |
| Not completed | 13 | 5 |
| Consent withdrawn by subject | 6 | 1 |
| Adverse event, non-fatal | 1 | 1 |
| Other | - | 2 |
| Progressive disease | 1 | - |
| Lost to follow-up | 5 | 1 |

Baseline characteristics

Reporting groups

| | |
|--|---------------|
| Reporting group title | VGX-3100 + EP |
| Reporting group description: Eligible subjects received three (3) 6-mg doses of VGX-3100 refrigerated formulation IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device. | |
| Reporting group title | Placebo + EP |
| Reporting group description: Eligible subjects received three (3) doses Placebo refrigerated formulation IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device. | |

| Reporting group values | VGX-3100 + EP | Placebo + EP | Total |
|---------------------------------------|---------------|--------------|-------|
| Number of subjects | 134 | 69 | 203 |
| Age categorical Units: Subjects | | | |
| <25 | 18 | 14 | 32 |
| ≥25 | 116 | 55 | 171 |
| Age continuous Units: years | | | |
| median | 30 | 31 | |
| full range (min-max) | 18 to 60 | 18 to 66 | - |
| Gender categorical Units: Subjects | | | |
| Female | 134 | 69 | 203 |
| Male | 0 | 0 | 0 |

Subject analysis sets

| | |
|--|-----------------------------|
| Subject analysis set title | ITT Analysis Set |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT analysis set consisted of 203 subjects who were randomly assigned to receive either VGX-3100 + EP (134 subjects) or placebo + EP (69 subjects). | |
| Subject analysis set title | mITT Analysis Set |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: The mITT set included all subjects who received at least one (1) dose of clinical trial treatment and who had the analysis endpoint of interest. Subjects in this sample were grouped to treatment as randomized. Analysis of the mITT set was considered supportive for the corresponding ITT set for the analysis of efficacy and also served as sensitivity analyses regarding missing data. | |
| Subject analysis set title | Per Protocol (PP) Set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The PP set was composed of subjects who received all doses of clinical trial treatments, had no protocol violations, and had the analysis endpoint of interest. | |
| Subject analysis set title | Safety Analysis Set |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety set included all subjects who received at least one (1) dose of clinical trial treatment.
Subjects were analyzed as to the treatment actually received.

| Reporting group values | ITT Analysis Set | mITT Analysis Set | Per Protocol (PP) Set |
|--|------------------|-------------------|-----------------------|
| Number of subjects | 203 | 198 | 183 |
| Age categorical Units: Subjects | | | |
| <25 | 32 | | |
| ≥25 | 171 | | |
| Age continuous Units: years median full range (min-max) | 30 18 to 66 | | |
| Gender categorical Units: Subjects | | | |
| Female | 203 | | |
| Male | 0 | | |

| Reporting group values | Safety Analysis Set | | |
|--|---------------------|--|--|
| Number of subjects | 202 | | |
| Age categorical Units: Subjects | | | |
| <25 | | | |
| ≥25 | | | |
| Age continuous Units: years median full range (min-max) | | | |
| Gender categorical Units: Subjects | | | |
| Female | | | |
| Male | | | |

End points

End points reporting groups

| | |
|--|-----------------------------|
| Reporting group title | VGX-3100 + EP |
| Reporting group description: Eligible subjects received three (3) 6-mg doses of VGX-3100 refrigerated formulation IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device. | |
| Reporting group title | Placebo + EP |
| Reporting group description: Eligible subjects received three (3) doses Placebo refrigerated formulation IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device. | |
| Subject analysis set title | ITT Analysis Set |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT analysis set consisted of 203 subjects who were randomly assigned to receive either VGX-3100 + EP (134 subjects) or placebo + EP (69 subjects). | |
| Subject analysis set title | mITT Analysis Set |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: The mITT set included all subjects who received at least one (1) dose of clinical trial treatment and who had the analysis endpoint of interest. Subjects in this sample were grouped to treatment as randomized. Analysis of the mITT set was considered supportive for the corresponding ITT set for the analysis of efficacy and also served as sensitivity analyses regarding missing data. | |
| Subject analysis set title | Per Protocol (PP) Set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The PP set was composed of subjects who received all doses of clinical trial treatments, had no protocol violations, and had the analysis endpoint of interest. | |
| Subject analysis set title | Safety Analysis Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety set included all subjects who received at least one (1) dose of clinical trial treatment. Subjects were analyzed as to the treatment actually received. | |

Primary: Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – Baseline Biomarker-positive Subjects (ITT population)

| | |
|---|--|
| End point title | Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – Baseline Biomarker-positive Subjects (ITT population) |
| End point description: Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 has been measured at Week 36 for baseline Biomarker-positive Subjects (ITT population). | |
| End point type | Primary |
| End point timeframe: At Week 36 | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | VGX-3100 + EP | Placebo + EP | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 4 | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Responders (n) | 6 | 0 | | |
| Responders (%) | 28.6 | 0 | | |

Statistical analyses

| | |
|--|------------------------------|
| Statistical analysis title | Statistical analysis |
| Statistical analysis description: | |
| A p-value of superiority was based on a test of risk difference and corresponding 95% confidence interval using the method of Miettinen and Nurminen. Superiority was to be concluded if the one-sided p-value was <0.025 and the corresponding lower bound of the 95% CI exceeded zero. | |
| Comparison groups | VGX-3100 + EP v Placebo + EP |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.115 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in Percentage |
| Point estimate | 28.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.6 |
| upper limit | 50.4 |

Primary: Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – Baseline Biomarker-positive Subjects (mITT population)

| | |
|---|---|
| End point title | Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – Baseline Biomarker-positive Subjects (mITT population) |
| End point description: | |
| Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 was measured at Week 36 for Baseline Biomarker-positive Subjects (mITT population). | |
| End point type | Primary |
| End point timeframe: | |
| At Week 36 | |

| End point values | VGX-3100 + EP | Placebo + EP | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 4 | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Subjects contributing analysis data | 19 | 4 | | |
| Responders (n) | 6 | 0 | | |
| Responders (%) | 31.6 | 0 | | |

Statistical analyses

| Statistical analysis title | Statistical analysis |
|---|------------------------------|
| Statistical analysis description: | |
| A p-value of superiority was based on a test of risk difference and corresponding 95% CI using the method of Miettinen and Nurminen. Superiority was concluded if the one-sided p-value was <0.025 and the corresponding lower bound of the 95% CI exceeded zero (0). | |
| Comparison groups | VGX-3100 + EP v Placebo + EP |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.101 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in Percentage |
| Point estimate | 31.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.2 |
| upper limit | 54.5 |

Primary: Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – Baseline Biomarker-positive Subjects (PP Population)

| | |
|---|---|
| End point title | Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – Baseline Biomarker-positive Subjects (PP Population) |
| End point description: | |
| Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 was measured at Week 36 for Baseline Biomarker-positive Subjects (PP Population). | |
| End point type | Primary |
| End point timeframe: | |
| At week 36 | |

| End point values | VGX-3100 + EP | Placebo + EP | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 3 | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Subjects contributing analysis data | 19 | 3 | | |
| Responders (n) | 6 | 0 | | |
| Responders (%) | 31.6 | 0 | | |

Statistical analyses

| Statistical analysis title | Statistical analysis |
|---|------------------------------|
| Statistical analysis description: | |
| A p-value of superiority was based on a test of risk difference and corresponding 95% CI using the method of Miettinen and Nurminen. Superiority was concluded if the one-sided p-value was <0.025 and the corresponding lower bound of the 95% CI exceeded zero (0). | |
| Comparison groups | VGX-3100 + EP v Placebo + EP |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.132 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in Percentage |
| Point estimate | 31.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.4 |
| upper limit | 54.5 |

Secondary: Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – All Subjects (ITT Population)

| | |
|--|--|
| End point title | Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – All Subjects (ITT Population) |
| End point description: | |
| Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 was measured at Week 36 – All Subjects (ITT Population). | |
| End point type | Secondary |
| End point timeframe: | |
| At week 36 | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | VGX-3100 + EP | Placebo + EP | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 69 | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Responders (n) | 37 | 6 | | |
| Responders (%) | 27.6 | 8.7 | | |

Statistical analyses

| | |
|--|------------------------------|
| Statistical analysis title | Statistical analysis |
| Statistical analysis description: | |
| A p-value of superiority was based on a test of risk difference and corresponding 95% confidence interval using the method of Miettinen and Nurminen. Superiority was to be concluded if the one-sided p-value was <0.025 and the corresponding lower bound of the 95% CI exceeded zero. | |
| Comparison groups | VGX-3100 + EP v Placebo + EP |
| Number of subjects included in analysis | 203 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in Percentage |
| Point estimate | 18.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.8 |
| upper limit | 28.6 |

Secondary: Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – All Subjects (mITT Population)

| | |
|------------------------|---|
| End point title | Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – All Subjects (mITT Population) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| At week 36 | |

| End point values | VGX-3100 + EP | Placebo + EP | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 130 | 68 | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Subjects contributing analysis data | 125 | 64 | | |
| Responders (n) | 37 | 6 | | |
| Responders (%) | 29.6 | 9.4 | | |

Statistical analyses

| Statistical analysis title | Statistical analysis |
|---|------------------------------|
| Statistical analysis description: | |
| A p-value of superiority was based on a test of risk difference and corresponding 95% CI using the method of Miettinen and Nurminen. Superiority was concluded if the one-sided p-value was <0.025 and the corresponding lower bound of the 95% CI exceeded zero (0). | |
| Comparison groups | VGX-3100 + EP v Placebo + EP |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in Percentage |

Secondary: Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – All Subjects (PP Population)

| | |
|------------------------|---|
| End point title | Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 – All Subjects (PP Population) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| At week 36 | |

| End point values | VGX-3100 + EP | Placebo + EP | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 61 | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Subjects contributing analysis data | 118 | 58 | | |
| Responders (n) | 37 | 6 | | |
| Responders (%) | 31.4 | 10.3 | | |

Statistical analyses

| Statistical analysis title | Statistical analysis |
|--|------------------------------|
| Statistical analysis description: A p-value of superiority was based on a test of risk difference and corresponding 95% CI using the method of Miettinen and Nurminen. Superiority was concluded if the one-sided p-value was <0.025 and the corresponding lower bound of the 95% CI exceeded zero (0). | |
| Comparison groups | VGX-3100 + EP v Placebo + EP |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in Percentage |
| Point estimate | 21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.3 |
| upper limit | 31.9 |

Secondary: Overview of Adverse Events (Safety Population)

| | |
|--|--|
| End point title | Overview of Adverse Events (Safety Population) |
| End point description: The incidence of TEAEs with onset within 7 days and 28 days after each clinical trial treatment was measured. The incidence if TEAEs was similar between the two (2) treatment groups. | |
| End point type | Secondary |
| End point timeframe: Within 7 days and 28 days after each clinical trial treatment | |

| End point values | VGX-3100 + EP | Placebo + EP | | |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 67 | | |
| Units: Subjects | | | | |
| Any AE | 131 | 67 | | |
| Any pretreatment AE | 25 | 12 | | |
| Any TEAE | 131 | 67 | | |
| Any serious TEAE | 9 | 9 | | |
| Any IP- or EP-related TEAE | 127 | 62 | | |
| Any IP- or EP-related serious TEAE | 0 | 0 | | |

| | | | | |
|--|----|---|--|--|
| Any TEAE with CTCAE ≥ 3 | 15 | 9 | | |
| Any IP- or EP-related TEAE with CTCAE ≥ 3 | 2 | 3 | | |
| Any TEAE of special interest | 0 | 0 | | |
| Any TEAE leading to treatment discontinuation | 2 | 1 | | |
| Any TEAE leading to death | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 7 days and 28 days after each clinical trial treatment

Adverse event reporting additional description:

The incidence of TEAEs with onset measured within 7 days and 28 days after each clinical trial treatment. None of the serious TEAEs reported in the VGX-3100 + EP group and in the placebo + EP group were related to IP or EP. No subject deaths were reported in either treatment group.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Eligible subjects received three (3) 6-mg doses of VGX-3100 refrigerated formulation IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device.

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

Reporting group description:

Eligible subjects received three (3) doses Placebo refrigerated formulation IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device.

| Serious adverse events | VGX-3100 + EP | Placebo + EP | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 134 (6.72%) | 9 / 67 (13.43%) | |
| 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) | | | |
| Adenocarcinoma of the cervix | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervix carcinoma stage 0 | | | |
| subjects affected / exposed | 4 / 134 (2.99%) | 3 / 67 (4.48%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 134 (1.49%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of the cervix | | | |
| subjects affected / exposed | 2 / 134 (1.49%) | 2 / 67 (2.99%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Ovarian rupture | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 67 (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 %

| Non-serious adverse events | VGX-3100 + EP | Placebo + EP | |
|---|--------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 131 / 134 (97.76%) | 67 / 67 (100.00%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 66 / 134 (49.25%) | 37 / 67 (55.22%) | |
| occurrences (all) | 66 | 37 | |
| Dizziness | | | |
| subjects affected / exposed | 8 / 134 (5.97%) | 2 / 67 (2.99%) | |
| occurrences (all) | 8 | 2 | |

| | | | |
|--|--------------------|------------------|--|
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 123 / 134 (91.79%) | 58 / 67 (86.57%) | |
| occurrences (all) | 123 | 58 | |
| Fatigue | | | |
| subjects affected / exposed | 56 / 134 (41.79%) | 33 / 67 (49.25%) | |
| occurrences (all) | 56 | 33 | |
| Injection site swelling | | | |
| subjects affected / exposed | 43 / 134 (32.09%) | 19 / 67 (28.36%) | |
| occurrences (all) | 43 | 19 | |
| Injection site erythema | | | |
| subjects affected / exposed | 36 / 134 (26.87%) | 15 / 67 (22.39%) | |
| occurrences (all) | 36 | 15 | |
| Injection site pruritus | | | |
| subjects affected / exposed | 33 / 134 (24.63%) | 22 / 67 (32.84%) | |
| occurrences (all) | 33 | 22 | |
| Injection site bruising | | | |
| subjects affected / exposed | 21 / 134 (15.67%) | 11 / 67 (16.42%) | |
| occurrences (all) | 21 | 11 | |
| Malaise | | | |
| subjects affected / exposed | 18 / 134 (13.43%) | 12 / 67 (17.91%) | |
| occurrences (all) | 18 | 12 | |
| Pyrexia | | | |
| subjects affected / exposed | 11 / 134 (8.21%) | 5 / 67 (7.46%) | |
| occurrences (all) | 11 | 5 | |
| Injection site haematoma | | | |
| subjects affected / exposed | 10 / 134 (7.46%) | 7 / 67 (10.45%) | |
| occurrences (all) | 10 | 7 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 36 / 134 (26.87%) | 17 / 67 (25.37%) | |
| occurrences (all) | 36 | 17 | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 4 / 134 (2.99%) | 5 / 67 (7.46%) | |
| occurrences (all) | 4 | 5 | |

| | | | |
|---|--|---|--|
| Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) | 56 / 134 (41.79%) 56 29 / 134 (21.64%) 29 2 / 134 (1.49%) 2 | 29 / 67 (43.28%) 29 14 / 67 (20.90%) 14 4 / 67 (5.97%) 4 | |
| Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 12 / 134 (8.96%) 12 8 / 134 (5.97%) 8 | 8 / 67 (11.94%) 8 1 / 67 (1.49%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 26 July 2018 | <ul style="list-style-type: none">• The number of participating sites and countries were updated.• A footnote was added to the primary hypothesis for the purpose of clarification and alignment with the timeframe for analysis.• The wording of secondary endpoints 1(a) and 1(b) were modified to more accurately state that all AEs, not just SAEs were to be reported through the entire duration that a subject was in the clinical trial.• Exploratory objective 2 and associated endpoints were removed.• The wording of secondary objective 8 was revised to reflect more clearly that immunology results were to be assessed relative to baseline levels.• For exploratory objective 3, DNA methylation was added to investigate as an additional potential biomarker.• Exploratory endpoint 4 was added to describe the association of the baseline tissue-based score derived using immunologic markers (immunoscore) to the Week 36 efficacy endpoint.• Text was clarified in the immunogenicity assessment, safety assessment, and trial population sections of the synopsis.• Human leukocyte antigen (HLA) testing was removed.• Revisions to the inclusion and exclusion criteria (synopsis, Sections 4.1, and 4.2)• Updates to the Schedule of Events table• General updates and clarifications <p>Additional minor grammatical and administrative changes were made throughout the document for improvement of general readability.</p> |
| 15 November 2018 | <ul style="list-style-type: none">• The EudraCT number was added to the protocol.• The number of participating countries was changed from 15 to 20. This change was made to the protocol synopsis.• The protocol was updated throughout to remove the digital photography procedure.• In Section 5.10.2 CELLECTRA™ 5PSP Device, wording was added to allow sites either to ship unused CELLECTRA™ 5PSP arrays back to Inovio or to destroy them on-site.• In Section 5.10.2 CELLECTRA™ 5PSP Device, text was updated as follows: upon completion or termination of 'the study' was replaced by 'Inovio's studies', to indicate that the Base Station and Handset must be returned to Inovio Pharmaceuticals, Inc after completion of Inovio's studies utilizing the CELLECTRA™ 5PSP device.• In Section 8.5.2.2 Immunogenicity, the Week 8 immunogenicity evaluation was removed from the text. |

| | |
|--------------|--|
| 01 June 2022 | <ul style="list-style-type: none"> • The primary population to which the primary objective was applied was changed from “all subjects” to “subjects defined as biomarker-positive at baseline,” as identified by microRNA (miRNA) profiling performed from peripheral blood prior to dosing with VGX-3100 (Section 6.10). This change was made in order to define a population of patients in whom VGX-3100 is more likely to be efficacious as defined by the primary endpoint of regression of cervical HSIL and clearance of HPV-16/18. • The protocol was revised to remove 4-quadrant biopsy as a potential procedure at Week 36 throughout the protocol. • Stopping Rules (Criteria for Pausing of Study) added to Data Safety Monitoring Board Charter version 3.0. • Updated acceptable contraception methods in Protocol Synopsis, Inclusion Criteria and Section 4.1, Inclusion Criteria. A footnote was added to clarify that use of condoms or condoms and spermicide are not acceptable forms of contraception. • Updated Table 1: Schedule of Events and Sections 6.1.1, 6.1.2, and 6.4.12, method of collection for cervical digene™ samples. Text was changed and updated the method of collection of cervical digene™ samples from swabs to brushes at screening, Day 0, Weeks 15, 28, and 36. • Clarifications on different sections added. • Administrative Changes. |
|--------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported