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 be 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) does 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	30		
full range (min-max)	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	56 / 134 (41.79%)	29 / 67 (43.28%)	
occurrences (all)	56	29	
Arthralgia			
subjects affected / exposed	29 / 134 (21.64%)	14 / 67 (20.90%)	
occurrences (all)	29	14	
Back pain			
subjects affected / exposed	2 / 134 (1.49%)	4 / 67 (5.97%)	
occurrences (all)	2	4	
Infections and infestations			
COVID-19			
subjects affected / exposed	12 / 134 (8.96%)	8 / 67 (11.94%)	
occurrences (all)	12	8	
Urinary tract infection			
subjects affected / exposed	8 / 134 (5.97%)	1 / 67 (1.49%)	
occurrences (all)	8	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2018	• 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 Additional minor grammatical and administrative changes were made throughout the document for improvement of general readability.
15 November 2018	• 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	• 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