Clinical trial results:
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	2016-002761-63
Trial protocol	GB LT FI DE CZ ES PT PL SK BE NL EE IT
Global end of trial date	06 April 2021
Results information	
Result version number	v2 (current)
This version publication date	24 January 2024
First version publication date	27 May 2022
Version creation reason	• New data added to full data set Outcome measures need updates
Summary attachment (see zip file)	Updated CSR synopsis (Inovio_HPV-301_Updated CSR Synopsis_v 2.1_17 Nov 2023.pdf) Errata 1 (Inovio_HPV-301-csr-errata-1_31Mar2023.pdf) Errata 2 (Inovio_HPV-301-csr-errata-2_17Nov2023.pdf)

Trial information

Trial identification	
Sponsor protocol code	HPV-301
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03185013
WHO universal trial number (UTN)	-
Other trial identifiers	US IND Number: 13683

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., HPV301ClinicalTeam@inovio.com
Scientific contact	Clinical Development, Inovio Pharmaceuticals, Inc., HPV301ClinicalTeam@inovio.com

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	06 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 April 2021
Global end of trial reached?	Yes
Global end of trial date	06 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the efficacy of VGX-3100 compared with placebo with respect to combined histopathologic regression of cervical high-grade squamous intraepithelial lesion (HSIL) and virologic clearance of human papillomavirus (HPV-16) and/or HPV-18.

Protection of trial subjects:

This protocol was implemented in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use harmonised tripartite guideline E6(R2): Good Clinical Practice. Written informed consent was to be obtained from each subject and/or from the subject’s legally authorized representative prior to screening into the clinical trial. Subjects were asked to complete a participant diary card during their clinical trial participation to record local and systemic adverse events for 7 days after each clinical trial treatment. Subjects were provided with the investigator emergency contact information and advised to report all AEs.

Background therapy:

Subjects might have used supportive medications for management of anxiety and pain due to treatment (topical anesthetic, mild sedative, analgesic).

Evidence for comparator:

Placebo (150 mM sodium chloride and 15 mM sodium citrate) plus electroporation (EP) with CELLECTRA™ 5PSP.

Actual start date of recruitment	28 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	17 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Peru: 2
Country: Number of subjects enrolled	Philippines: 1
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	Thailand: 12

Country: Number of subjects enrolled	United States: 56
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Estonia: 36
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Lithuania: 22
Worldwide total number of subjects	201
EEA total number of subjects	106

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)	201
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 96 study centres in 20 countries from 28 June 2017 to 06 April 2021.

Pre-assignment

Screening details:

A total of 201 subjects with HPV-16 and/or HPV-18 related HSIL of the cervix were randomised in this study, 138 in VGX-3100 + EP and 63 in Placebo + EP.

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

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. No personnel directly involved with the clinical trial was to be unblinded. The investigator may have requested to unblind a subject's treatment assignment in case of an emergency or serious medical condition.

Arms

Are arms mutually exclusive?	Yes
Arm title	VGX-3100 + EP

Arm description:

Subjects received three intramuscular (IM) injections of 6 milligram (mg) (in 1 milliliter [mL]) VGX-3100 followed by EP using the CELLECTRA™-5PSP device 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	Injection , Intramuscular use

Dosage and administration details:

6-mg dose of VGX-3100 drug product was delivered IM followed by EP. VGX-3100 drug product was provided as a solution containing 6 mg in 150 mM sodium chloride and 15 mM sodium citrate. The IP was delivered using the CELLECTRA™ 5PSP device. The device consisted of the following components: 1) Base Station; 2) Handset; and 3) Sterile single-use Array (for accepting the IP cartridge). The first clinical trial treatment was administered on Day 0, the second at Week 4, and the third (final) at Week 12.

Arm title	Placebo + EP

Arm description:

Subjects received three IM injections of 1 mL VGX-3100 matching placebo followed by EP using the CELLECTRA™-5PSP device on Day 0, Week 4, and Week 12.

Arm type	Placebo + EP
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Subjects received 1 mL placebo IM followed by EP. Placebo was delivered using the CELLECTRA™ 5PSP device. The device consisted of the following components: 1) Base Station; 2) Handset; and 3) Sterile single-use Array (for accepting the IP cartridge). The first clinical trial treatment was administered on Day 0, the second at Week 4, and the third (final) at Week 12.

Number of subjects in period 1	VGX-3100 + EP	Placebo + EP
Started	138	63
Completed	117	56
Not completed	21	7
Physician decision	1	-
Adverse Event	1	-
Progressive Disease	1	-
Withdrawal by Subject	5	3
Lost to follow-up	8	2
Reason not Specified	3	2
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	VGX-3100 + EP
Reporting group description:	
Subjects received three intramuscular (IM) injections of 6 milligram (mg) (in 1 milliliter [mL]) VGX-3100 followed by EP using the CELLECTRA™-5PSP device on Day 0, Week 4, and Week 12.	
Reporting group title	Placebo + EP
Reporting group description:	
Subjects received three IM injections of 1 mL VGX-3100 matching placebo followed by EP using the CELLECTRA™-5PSP device on Day 0, Week 4, and Week 12.	

Reporting group values	VGX-3100 + EP	Placebo + EP	Total
Number of subjects	138	63	201
Age categorical Units: Subjects			
Adults (18-64 years)	138	63	201
Age continuous Units: years			
arithmetic mean	31.3	31.9	
standard deviation	± 6.53	± 6.08	-
Gender categorical Units: Subjects			
Female	138	63	201
Male	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	22	9	31
Not Hispanic or Latino	112	54	166
Unknown or Not Reported	4	0	4
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	9	6	15
Black or African American	8	5	13
Native Hawaiian or Other Pacific Islander	0	1	1
White	109	46	155
Other	10	2	12
Multiple	1	0	1
Missing	1	2	3

Subject analysis sets	
Subject analysis set title	Intent-to-Treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent-to-Treat (ITT) population included all subjects who were randomized.	
Subject analysis set title	Modified ITT (mITT)

Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intent-to-Treat (mITT) population included all subjects who received at least one (1) dose of clinical trial treatment and who had the analysis endpoint of interest.

Subject analysis set title	Per-Protocol (PP) Set
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol (PP) Set was comprised 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 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.

Reporting group values	Intent-to-Treat (ITT)	Modified ITT (mITT)	Per-Protocol (PP) Set
Number of subjects	201	197	184
Age categorical Units: Subjects			
Adults (18-64 years)	201	197	184
Age continuous Units: years			
arithmetic mean	31.5		
standard deviation	± 6.38	±	±
Gender categorical Units: Subjects			
Female	201	197	184
Male	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Race Units: Subjects			
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Other Pacific Islander			
White			
Other			
Multiple			
Missing			

Reporting group values	Safety Set		
Number of subjects	199		
Age categorical Units: Subjects			
Adults (18-64 years)	199		

Age continuous Units: years arithmetic mean standard deviation	 ±		
Gender categorical Units: Subjects			
Female Male	199 0		
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Other Multiple Missing			

End points

End points reporting groups

Reporting group title	VGX-3100 + EP

Reporting group description:

Subjects received three intramuscular (IM) injections of 6 milligram (mg) (in 1 milliliter [mL]) VGX-3100 followed by EP using the CELLECTRA™-5PSP device on Day 0, Week 4, and Week 12.

Reporting group title	Placebo + EP

Reporting group description:

Subjects received three IM injections of 1 mL VGX-3100 matching placebo followed by EP using the CELLECTRA™-5PSP device on Day 0, Week 4, and Week 12.

Subject analysis set title	Intent-to-Treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intent-to-Treat (ITT) population included all subjects who were randomized.

Subject analysis set title	Modified ITT (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intent-to-Treat (mITT) population included all subjects who received at least one (1) dose of clinical trial treatment and who had the analysis endpoint of interest.

Subject analysis set title	Per-Protocol (PP) Set
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol (PP) Set was comprised 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 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.

Primary: Percentage of Subjects With No Evidence of Cervical HSIL on Histology and No Evidence of HPV-16 and/or HPV-18 in Cervical Samples

End point title	Percentage of Subjects With No Evidence of Cervical HSIL on Histology and No Evidence of HPV-16 and/or HPV-18 in Cervical Samples

End point description:

Subjects with no histologic (i.e., biopsies or excisional treatment) evidence of cervical HSIL, no evidence of HPV-16 and/or HPV-18 at the Week 36 time frame, and subjects in which excision or biopsy sample was not obtained between the initial dose up to Week 36 were considered to be responders. No evidence of HSIL was defined by histology as negative, squamous atypia, or low-grade intraepithelial lesion (LSIL). Cervical samples for HPV-16 and/or HPV-18 were collected using the ThinPrep®. ITT population included all subjects who were randomised.

End point type	Primary

End point timeframe:

Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	63		
Units: percentage of subjects				
number (not applicable)	22.5	11.1		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
Superiority was concluded if the one-sided p-value was <0.025 and the corresponding lower bound of the 95% confidence interval (CI) exceeded zero (0).	
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029 [1]
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	21.2

Notes:

[1] - One-sided p-value

Primary: Histopathological Regression of Cervical HSIL and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 (mITT Population)

End point title	Histopathological Regression of Cervical HSIL and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 (mITT Population)

End point description:

Subjects with no histologic (i.e., biopsies or excisional treatment) evidence of cervical HSIL, no evidence of HPV-16 and/or HPV-18 at the Week 36 time frame, and subjects in which excision or biopsy sample was not obtained between the initial dose up to Week 36 were considered to be responders. No evidence of HSIL was defined by histology as negative, squamous atypia, or low-grade intraepithelial lesion (LSIL). Cervical samples for HPV-16 and/or HPV-18 were collected using the ThinPrep®. mITT population included all subjects who received at least one (1) dose of clinical trial treatment and who had the analysis endpoint of interest. Analyses of primary efficacy endpoint with the mITT set served as sensitivity analyses and were considered supportive of the corresponding analysis with the ITT set.

End point type	Primary

End point timeframe:

Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	63		
Units: subjects				
number (not applicable)				
Subjects contributing analysis data (n)	131	62		
Responders (n)	31	7		
Responders (%)	23.7	11.3		

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

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	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022 [2]
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	22.5

Notes:

[2] - One-sided p-value

Primary: Histopathological Regression of Cervical HSIL and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 (PP Population)

End point title	Histopathological Regression of Cervical HSIL and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 (PP Population)

End point description:

Subjects with no histologic (i.e., biopsies or excisional treatment) evidence of cervical HSIL, no evidence of HPV-16 and/or HPV-18 at the Week 36 time frame, and subjects in which excision or biopsy sample was not obtained between the initial dose up to Week 36 were considered to be responders. No evidence of HSIL was defined by histology as negative, squamous atypia, or low-grade intraepithelial lesion (LSIL). Cervical samples for HPV-16 and/or HPV-18 were collected using the ThinPrep®. PP Set was comprised of subjects who received all doses of clinical trial treatments, had no protocol violations, and had the analysis endpoint of interest. Analyses of primary efficacy endpoint with the PP set served as sensitivity analyses and were considered supportive of the corresponding analysis with the ITT set.

End point type	Primary

End point timeframe:

Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	60		
Units: subjects				
number (not applicable)				
Subjects contributing analysis data	122	60		
Responders (n)	30	7		
Responders (%)	24.6	11.7		

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

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	Placebo + EP v VGX-3100 + EP
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [3]
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	12.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	23.5

Notes:

[3] - One-sided p-value

Secondary: Number of Subjects With Any Adverse Events (AEs) and Serious Adverse Events (SAEs) Following Investigational Treatment for the Duration of the Study

End point title	Number of Subjects With Any Adverse Events (AEs) and Serious Adverse Events (SAEs) Following Investigational Treatment for the Duration of the Study

End point description:

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as AEs. An SAE is any experience that suggested a significant hazard, contraindication, side effect, or precaution, and fulfilled any of the following criteria: fatal (resulted in death), life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was medically significant or required intervention to prevent any of the tother outcomes listed here. Safety set was used.

End point type	Secondary

End point timeframe:

From baseline up to Week 88

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	62		
Units: subjects				
Number of Subjects with any AE	131	61		
Number of Subjects with any SAE	13	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With No Evidence of Cervical HSIL on Histology

End point title	Percentage of Subjects With No Evidence of Cervical HSIL on Histology

End point description:

Subjects with no histologic (i.e., biopsies or excisional treatment) evidence of cervical HSIL at Week 36 and subjects in which an excision or biopsy sample was not obtained between the initial dose up to Week 36 were considered to be responders. No evidence of HSIL was defined by histology as negative, squamous atypia, or LSIL. ITT population included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	63		
Units: percentage of subjects				
number (not applicable)	31.9	19.0		

Statistical analyses

Statistical analysis title	VGX-3100 + Electroporation (EP), Placebo + EP
Comparison groups	VGX-3100 + EP v Placebo + EP

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[4]
Parameter estimate	Difference in percentage
Point estimate	12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	24.5

Notes:

[4] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Secondary: Percentage of Subjects With No Evidence of HPV-16 and/or HPV-18 in Cervical Samples by Type Specific HPV Testing

End point title	Percentage of Subjects With No Evidence of HPV-16 and/or HPV-18 in Cervical Samples by Type Specific HPV Testing

End point description:

Subjects with no evidence of HPV-16 and/or HPV-18 at the Week 36 time frame and subjects in which an excision or biopsy sample was not obtained between the initial dose up to Week 36 were considered to be responders. Cervical samples for HPV-16 and/or HPV-18 were collected using the ThinPrep®. ITT population included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	63		
Units: percentage of subjects				
number (not applicable)	34.1	15.9		

Statistical analyses

Statistical analysis title	VGX-3100 + Electroporation (EP), Placebo + EP
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[5]
Parameter estimate	Difference in percentage
Point estimate	18.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.1
upper limit	29.4

Notes:

[5] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Secondary: Percentage of Subjects With No Evidence of LSIL or HSIL on Histology

End point title	Percentage of Subjects With No Evidence of LSIL or HSIL on Histology

End point description:

Subjects with no histologic evidence of cervical HSIL, squamous atypia, or LSIL at the Week 36 time frame and subjects in which an excision or biopsy sample was not obtained between the initial dose up to Week 36 were considered to be responders. No evidence of HSIL was defined as no evidence of cervical squamous intraepithelial neoplasia 1 (CIN1), CIN2, or CIN3 on biopsies or excisional treatment. ITT population included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	63		
Units: percentage of subjects				
number (not applicable)	24.6	11.1		

Statistical analyses

Statistical analysis title	VGX-3100 + Electroporation (EP), Placebo + EP
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	Difference in percentage
Point estimate	13.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	23.5

Notes:

[6] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Secondary: Percentage of Subjects With No Evidence of LSIL or HSIL and No Evidence of HPV-16 and/or HPV-18

End point title	Percentage of Subjects With No Evidence of LSIL or HSIL and No Evidence of HPV-16 and/or HPV-18

End point description:

Subjects with no histologic evidence of cervical HSIL, squamous atypia, and LSIL, no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at the Week 36 time, and subjects in which an excision or biopsy sample was not obtained between initial dose up to Week 36 were considered to be responders.

No evidence of HSIL was defined as no evidence of CIN1, CIN2, or CIN3 on biopsies or excisional treatment. ITT population included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	63		
Units: percentage of subjects				
number (not applicable)	18.1	6.3		

Statistical analyses

Statistical analysis title	VGX-3100 + Electroporation (EP), Placebo + EP
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[7]
Parameter estimate	Difference in percentage
Point estimate	11.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	20.3

Notes:

[7] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Secondary: Percentage of Subjects With No Progression of Cervical HSIL to Cervical Carcinoma

End point title	Percentage of Subjects With No Progression of Cervical HSIL to Cervical Carcinoma

End point description:

Subjects with no histologic evidence of cervical Adenocarcinoma in situ or cervical carcinoma at the Week 36 timeframe relative to baseline and subjects in which an excision or biopsy sample was not obtained between initial dose up to Week 36 were considered as responders. ITT population included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	63		
Units: percentage of subjects				
number (not applicable)	84.1	85.7		

Statistical analyses

Statistical analysis title	VGX-3100 + Electroporation (EP), Placebo + EP
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[8]
Parameter estimate	Difference in percentage
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	10.3

Notes:

[8] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Secondary: Percentage of Subjects Who Have Cleared HPV-16 and/or HPV-18 in Non-cervical Anatomic Locations

End point title	Percentage of Subjects Who Have Cleared HPV-16 and/or HPV-18 in Non-cervical Anatomic Locations

End point description:

Subjects with no evidence of HPV-16 and/or HPV-18 on specimens from noncervical anatomic locations (oropharynx, vagina and intra-anal) at the Week 36 time frame were considered as responder. ITT population included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	63		
Units: percentage of subjects				
number (not applicable)	20.3	9.5		

Statistical analyses

Statistical analysis title	VGX-3100 + Electroporation (EP), Placebo + EP
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[9]
Parameter estimate	Difference in percentage
Point estimate	10.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	20.1

Notes:

[9] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Secondary: Levels of Serum Anti-HPV-16 and Anti-HPV-18 Antibody Concentrations

End point title	Levels of Serum Anti-HPV-16 and Anti-HPV-18 Antibody Concentrations

End point description:

A standardized binding enzyme-linked immunosorbent assay (ELISA) was performed to measure the anti–HPV-16/18 antibody response induced by VGX-3100. mITT population included all subjects who received at least one dose of clinical trial treatment and who had the analysis endpoint of interest. Overall number analyzed is the number of subjects with data available for analysis. Number analyzed is the number of subjects with data available for analysis at the specified timepoints.

End point type	Secondary

End point timeframe:

Week 15 and Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	61		
Units: reciprocal endpoint titer				
median (full range (min-max))				
HPV-16 E7 at Week 15 (n=128,61)	225.0 (1 to 18225)	1.0 (1 to 6075)		
HPV-16 E7 at Week 36 (n=128,58)	1.0 (1 to 18225)	1.0 (1 to 6075)		
HPV-18 E7 at Week 15 (n=128,61)	2025.0 (1 to 18225)	1.0 (1 to 18225)		
HPV-18 E7 at Week 36 (n=128,58)	225.0 (1 to 18225)	1.0 (1 to 2025)		

Statistical analyses

Statistical analysis title	Week 15: HPV-16 E7
Comparison groups	VGX-3100 + EP v Placebo + EP

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority[10]
Parameter estimate	Difference in median
Point estimate	224
Confidence interval	
level	95 %
sides	2-sided
lower limit	24
upper limit	224

Notes:

[10] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	Week 36: HPV-16 E7
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority[11]
Parameter estimate	Difference in median
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[11] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	Week 15: HPV-18 E7
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority[12]
Parameter estimate	Difference in median
Point estimate	2024
Confidence interval	
level	95 %
sides	2-sided
lower limit	2000
upper limit	6050

Notes:

[12] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	Week 36: HPV-18 E7
Comparison groups	VGX-3100 + EP v Placebo + EP

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority[13]
Parameter estimate	Difference in median
Point estimate	224
Confidence interval	
level	95 %
sides	2-sided
lower limit	74
upper limit	674

Notes:

[13] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Secondary: Change From Baseline in Interferon-Gamma Response Magnitude

End point title	Change From Baseline in Interferon-Gamma Response Magnitude

End point description:

Assessment of cellular immune activity occurred via the application of the Interferon-γ enzyme-linked immunosorbent spot (IFN-γ ELISpot). Peripheral blood mononuclear cells (PBMCs) isolated from whole blood sample were used for analysis. mITT population included all subjects who received at least one dose of clinical trial treatment and who had the analysis endpoint of interest. Overall number analysed is the number of subjects with data available for analysis. Number analysed is the number of subjects with data available for analysis at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline; Week 15 and Week 36

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	54		
Units: spot forming units (SFU)/106 PBMC				
median (full range (min-max))				
HPV-16 E6: Baseline (n=116, 54)	0.83 (0.0 to 40.0)	0.0 (0.0 to 16.7)		
HPV-16 E6:Change from Baseline at Week15(n=102,45)	13.33 (0.0 to 446.7)	0.0 (0.0 to 13.3)		
HPV-16 E6:Change from Baseline at Week36(n=90,41)	8.33 (0.0 to 780.0)	0.00 (0.0 to 25.0)		
HPV-16 E7: Baseline (n=116, 54)	0.0 (0.0 to 53.3)	0.0 (0.0 to 83.3)		
HPV-16 E7:Change from Baseline at Week15(n=102,45)	10.83 (0.0 to 213.3)	0.0 (0.0 to 13.3)		
HPV-16 E7:Change from Baseline at Week36(n=90,41)	7.50 (0.0 to 81.7)	0.0 (0.0 to 8.3)		
HPV-18 E6: Baseline (n=116,54)	0.0 (0.0 to 10.0)	0.0 (0.0 to 20.0)		
HPV-18 E6:Change from Baseline at Week15(n=102,45)	50.83 (0.0 to 1910.0)	0.0 (0.0 to 6.7)		
HPV-18 E6:Change from Baseline at Week36(n=90,41)	38.33 (0.0 to 1031.7)	0.0 (0.0 to 23.3)		

HPV-18 E7: Baseline (n=116,54)	0.0 (0.0 to 11.7)	0.0 (0.0 to 91.7)		
HPV-18 E7:Change from Baseline at Week15(n=102,45)	14.17 (0.0 to 251.7)	0.00 (0.0 to 20.0)		
HPV-18 E7:Change from Baseline at Week36(n=90,41)	10.00 (0.0 to 508.3)	0.00 (0.0 to 6.7)		

Statistical analyses

Statistical analysis title	HPV-16 E6: Week 15
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[14]
Parameter estimate	Difference in median
Point estimate	13.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.33
upper limit	20

Notes:

[14] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	HPV-16 E6: Week 36
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[15]
Parameter estimate	Difference in median
Point estimate	8.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.33
upper limit	11.67

Notes:

[15] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	HPV-16 E7: Week 15
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[16]
Parameter estimate	Difference in median
Point estimate	10.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	15

Notes:

[16] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	HPV-16 E7: Week 36
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[17]
Parameter estimate	Difference in median
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.67
upper limit	10

Notes:

[17] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	HPV-18 E6: Week 15
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[18]
Parameter estimate	Difference in median
Point estimate	50.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.67
upper limit	66.67

Notes:

[18] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	HPV-18 E6: Week 36
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[19]
Parameter estimate	Difference in median
Point estimate	38.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.33
upper limit	51.67

Notes:

[19] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	HPV-18 E7: Week 15
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[20]
Parameter estimate	Difference in median
Point estimate	14.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.67
upper limit	18.33

Notes:

[20] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	HPV-18 E7: Week 36
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[21]
Parameter estimate	Difference in median
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	15

Notes:

[21] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Secondary: Change From Baseline (CFB) in Flow Cytometry Response Magnitude

End point title	Change From Baseline (CFB) in Flow Cytometry Response Magnitude

End point description:

Assessment of cellular immune activity was measured using the application flow cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay examines the following external cellular markers: CD3, CD4, CD8 (T cell identification), CD137, CD38 and CD69 (T cell activation markers) as well as PD-1 (exhaustion/activation marker). Here change from baseline in CD8+CD137+Perforin+, CD8+CD38+Perforin+ and CD8+CD69+Perforin+ are reported. mITT population included all subjects who received at least one dose of clinical trial treatment and who had the analysis endpoint of interest. Overall number analysed is the number of subjects with data available for analysis. Number analysed is the number of subjects with data available for analysis at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	58		
Units: percentage of PBMC				
median (full range (min-max))				
CD8+CD137+Perforin+: Baseline (n=114, 58)	0.004 (0.00 to 0.15)	0.001 (0.00 to 0.22)		
CD8+CD137+Perforin+:CFB at Week 15 (n=106, 42)	0.035 (0.00 to 0.044)	0.000 (0.00 to 0.10)		
CD8+CD38+Perforin+: Baseline (n=114, 48)	0.000 (0.00 to 0.21)	0.000 (0.00 to 0.12)		
CD8+CD38+Perforin+: CFB at Week 15 (n=106, 42)	0.011 (0.00 to 0.23)	0.000 (0.00 to 0.10)		
CD8+CD69+Perforin+: Baseline (n=114, 48)	0.009 (0.00 to 0.11)	0.001 (0.00 to 0.13)		
CD8+CD69+Perforin+: CFB at Week 15 (n=106, 42)	0.044 (0.00 to 0.37)	0.000 (0.00 to 0.07)		

Statistical analyses

Statistical analysis title	Parameter: CD8+CD137+Perforin+
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority[22]
Parameter estimate	Difference in median
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.046

Notes:

[22] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	Parameter: CD8+CD38+Perforin+
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority[23]
Parameter estimate	Difference in median
Point estimate	0.011

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.014

Notes:

[23] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Statistical analysis title	Parameter: CD8+CD69+Perforin+
Comparison groups	VGX-3100 + EP v Placebo + EP
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority[24]
Parameter estimate	Difference in median
Point estimate	0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.058

Notes:

[24] - Superiority was concluded if the lower bound of the 95% CI exceeded 0.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to Week 88

Adverse event reporting additional description:

Safety set included all subjects who received at least one dose of clinical trial treatment. One subject received mixed treatment and was excluded from the safety analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	VGX-3100 + EP

Reporting group description:

Subjects received three IM injections of 6 mg (in 1 mL) VGX-3100 followed by EP using the CELLECTRA™-5PSP device on Day 0, Week 4, and Week 12.

Reporting group title	Placebo + EP

Reporting group description:

Subjects received three IM injections of 1 mL VGX-3100 matching placebo followed by EP using the CELLECTRA™-5PSP device 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	13 / 136 (9.56%)	6 / 62 (9.68%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenosquamous carcinoma of the cervix			
subjects affected / exposed	0 / 136 (0.00%)	1 / 62 (1.61%)	
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	3 / 136 (2.21%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the cervix			

subjects affected / exposed	5 / 136 (3.68%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ligament injury			
subjects affected / exposed	1 / 136 (0.74%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 136 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 136 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	0 / 136 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diaphragmatic hernia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	1 / 62 (1.61%)	
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 / 136 (0.74%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 136 (0.74%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Kidney infection			
subjects affected / exposed	1 / 136 (0.74%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 136 (0.74%)	0 / 62 (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 / 136 (96.32%)	61 / 62 (98.39%)	
Nervous system disorders			
Headache			
subjects affected / exposed	45 / 136 (33.09%)	19 / 62 (30.65%)	
occurrences (all)	67	29	
General disorders and administration site conditions			
Injection-site pain			
subjects affected / exposed	107 / 136 (78.68%)	50 / 62 (80.65%)	
occurrences (all)	246	114	
Fatigue			
subjects affected / exposed	39 / 136 (28.68%)	17 / 62 (27.42%)	
occurrences (all)	65	29	
Injection-site erythema			

subjects affected / exposed	34 / 136 (25.00%)	14 / 62 (22.58%)	
occurrences (all)	64	28	
Injection-site pruritus			
subjects affected / exposed	34 / 136 (25.00%)	14 / 62 (22.58%)	
occurrences (all)	53	21	
Injection-site swelling			
subjects affected / exposed	28 / 136 (20.59%)	15 / 62 (24.19%)	
occurrences (all)	69	29	
Injection-site bruising			
subjects affected / exposed	14 / 136 (10.29%)	9 / 62 (14.52%)	
occurrences (all)	26	11	
Malaise			
subjects affected / exposed	11 / 136 (8.09%)	5 / 62 (8.06%)	
occurrences (all)	17	7	
Injection-site haematoma			
subjects affected / exposed	9 / 136 (6.62%)	6 / 62 (9.68%)	
occurrences (all)	12	10	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	25 / 136 (18.38%)	11 / 62 (17.74%)	
occurrences (all)	36	13	
Abdominal pain			
subjects affected / exposed	8 / 136 (5.88%)	2 / 62 (3.23%)	
occurrences (all)	11	2	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	29 / 136 (21.32%)	15 / 62 (24.19%)	
occurrences (all)	47	22	
Arthralgia			
subjects affected / exposed	13 / 136 (9.56%)	7 / 62 (11.29%)	
occurrences (all)	17	10	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 136 (9.56%)	4 / 62 (6.45%)	
occurrences (all)	15	4	
Bacterial vaginosis			

subjects affected / exposed	9 / 136 (6.62%)	3 / 62 (4.84%)	
occurrences (all)	10	3	
Vulvovaginal candidiasis			
subjects affected / exposed	9 / 136 (6.62%)	3 / 62 (4.84%)	
occurrences (all)	9	3	
Urinary tract infection			
subjects affected / exposed	7 / 136 (5.15%)	4 / 62 (6.45%)	
occurrences (all)	7	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2016	The main changes in Protocol version 2.0 include the following: • Added rationale for selection of nonfrozen formulation for Phase 3 clinical trial. • Added additional background information to Section 2 Study Design. • Clarified inclusion and exclusion criteria. • Administrative changes made throughout the protocol for clarification, that did not significantly affect the safety of subjects, clinical trial scope, or scientific quality of the protocol.
10 June 2016	The main changes in Protocol version 2.1 include the following: • Administrative and formatting changes were made to protocol version 2.0 dated 06Jun2016 resulting in protocol version 2.1 dated 10Jun2016.
23 September 2016	The main changes in Protocol version 3.0 include the following: • Name of the investigational product (IP) was changed from VGX-3100X to VGX-3100. The term VGX-3100 as used in protocol version 3.0 denoted 3.0 ± 0.2 mg/mL pGX3001 bulk plasmid and 3.0 ± 0.2 mg/mL pGX3002 bulk plasmid in SSC buffer, refrigerated formulation. • The population for the primary analysis for the clinical trial was changed from mITT based on complete data to intent-to-treat (ITT) analysis. Based on this change, the number of subjects to be enrolled in the clinical trial was now 198 instead of 165. • Modifications in objectives and endpoints • Modifications in inclusion and exclusion criteria • Modifications to the clinical trial evaluations • Section 2.1.3 Definition of Responder and Nonresponde • Added information on supplementation of subjects in case more than 10% of subjects randomly assigned to clinical trial treatment discontinued prior to the Week 36 primary endpoint procedure. • Section 5.7 Return and Destruction of Investigational Product • Section 6.1.1 Screening Evaluations • Section 6.15.1 Prohibited Concomitant Medications and Treatments • Added that progression of HSIL to microinvasive or invasive squamous cell carcinoma should be reported as an SAE. • Section 7.3.1 was modified to replace the term “events requiring expedited reporting” to “adverse events of special interest (AESI)”. Added clarification on reporting requirements to sponsor. • Section 7.4.2 was updated to reflect change in reporting contact details in event of SAE. • Section 8 Statistical Analysis section • Section 9.4.2 Pathology Adjudication Committee • Additional administrative clarifications were made to the protocol that did not significantly affect the safety of subjects, clinical trial scope, or scientific quality of the protocol.

29 March 2018	The main changes in Protocol version 4.0 include the following: • Modifications and updates to the hypothesis, objectives, and endpoints • Revisions to the inclusion and exclusion criteria • Updates were made to the Schedule of Events table to align with the protocol text and above-mentioned changes to the clinical trial endpoints and inclusion and exclusion criteria. • General updates and clarifications • Section 7.3 (Safety and Toxicity Management) was modified to align with safety assessments as stated in the section describing clinical trial design of clinical protocol synopsis. • Section 8 (Statistical Analysis Plan) was revised to align with the changes made to objectives and endpoints. • Section 9.4.2 (Pathology Adjudication Committee) was modified to refer to the PAC charter, which had the most current information regarding the PAC review process. • The PDC was unchanged but was removed from the Appendix since the PDC was a separate document. • Additional minor grammatical and administrative changes were made throughout the document for improving the general readability of the protocol.
20 November 2019	The main changes in Protocol version 5.0 include the following: • Human leukocyte antigen (HLA) testing and associated exploratory endpoint 2 was removed from the protocol in consideration of the HPV-003 clinical trial results which showed no clear association of HLA background as a predictor of response. • Group-level unblinded (VGX-3100, placebo) summaries and analyses of efficacy were to be produced once the primary endpoint Week 36 visit data were collected for all subjects. • The stopping rules outlined in Section 7.3.2, Stopping Rules (Criteria for Pausing of Study), were clarified to focus on unexpected, verified events and not include events that were already described as known adverse drug reactions. • Additional administrative clarifications were made to the protocol that did not significantly affect the safety of subjects, clinical trial scope, or scientific quality of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported