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	v1
This version publication date	27 May 2022
First version publication date	27 May 2022

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 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	03 March 2022
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 HSIL and virologic clearance of 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 EP (electroporation) with CELLECTRA™ 5PSP.

Actual start date of recruitment	28 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	88 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:

A total of 201 subjects were randomly assigned to receive either VGX-3100 + EP (138 subjects) or placebo + EP (63 subjects) within 10 weeks of first dose of clinical trial treatment (Day 0).

Pre-assignment

Screening details:

All screening evaluations were to be completed within 10 weeks of first dose of clinical trial treatment (Day 0), except for the safety laboratory assessments, which were to be performed within 45 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

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:

Eligible subjects received three 6-mg doses of VGX-3100 refrigerated formulation provided as a solution followed immediately by electroporation (EP) with the CELLECTRA™ 5PSP device. Treatment was administered over 12 weeks.

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:

Eligible subjects received three placebo, followed immediately by electroporation (EP) with the CELLECTRA™ 5PSP device. Treatment was administered over 12 weeks.

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	129	61
Not completed	9	2
Consent withdrawn by subject	1	1
Randomized, but not treated	2	-
Other	-	1
Pregnancy	2	-
Progressive disease	2	-
Lost to follow-up	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	VGX-3100 + EP
Reporting group description:	
Eligible subjects received three 6-mg doses of VGX-3100 refrigerated formulation provided as a solution followed immediately by electroporation (EP) with the CELLECTRA™ 5PSP device. Treatment was administered over 12 weeks.	
Reporting group title	Placebo + EP
Reporting group description:	
Eligible subjects received three placebo, followed immediately by electroporation (EP) with the CELLECTRA™ 5PSP device. Treatment was administered over 12 weeks.	

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			
median	30	31	
full range (min-max)	20 to 55	23 to 48	-
Gender categorical			
Units: Subjects			
Female	138	63	201
Male	0	0	0

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) set included all subjects who were randomized. Subjects in this sample were grouped to treatment as randomized. The ITT set was used for the primary analysis of efficacy in this clinical trial.	
Subject analysis set title	Modified ITT (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Modified Intent-to-Treat (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. The analysis of the mITT set 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:	
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. Subjects in this sample were grouped to treatment as randomized. Analyses on the PP set was considered supportive of the corresponding ITT set for the analysis of efficacy. The analysis of PP Set also served as sensitivity analyses regarding early intervention (i.e, intervention before the Week 36 timeframe).	
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. Subjects were analyzed as to the treatment they actually received.

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 median full range (min-max)	 30 20 to 55		
Gender categorical Units: Subjects			
Female	201	197	184
Male	0	0	0

Reporting group values	Safety Set		
Number of subjects	199		
Age categorical Units: Subjects			
Adults (18-64 years)	199		
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female	199		
Male	0		

End points

End points reporting groups

Reporting group title	VGX-3100 + EP

Reporting group description:

Eligible subjects received three 6-mg doses of VGX-3100 refrigerated formulation provided as a solution followed immediately by electroporation (EP) with the CELLECTRA™ 5PSP device. Treatment was administered over 12 weeks.

Reporting group title	Placebo + EP

Reporting group description:

Eligible subjects received three placebo, followed immediately by electroporation (EP) with the CELLECTRA™ 5PSP device. Treatment was administered over 12 weeks.

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

Subject analysis set description:

Intent-to-Treat (ITT) set included all subjects who were randomized. Subjects in this sample were grouped to treatment as randomized. The ITT set was used for the primary analysis of efficacy in this clinical trial.

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

Subject analysis set description:

Modified Intent-to-Treat (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. The analysis of the mITT set 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:

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. Subjects in this sample were grouped to treatment as randomized. Analyses on the PP set was considered supportive of the corresponding ITT set for the analysis of efficacy. The analysis of PP Set also served as sensitivity analyses regarding early intervention (i.e, intervention before the Week 36 timeframe).

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. Subjects were analyzed as to the treatment they actually received.

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

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

End point description:

The percentage of responders in each treatment group was based on the histopathological regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36 and it was summarized for the 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	138	63		
Units: subjects				
number (not applicable)				
Responders (n)	31	7		
Responders (%)	22.5	11.1		

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

A p-value of superiority based on a test of risk difference and corresponding 95% confidence interval (CI) using the method of Miettinen and Nurminen were computed. 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	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029 [1]
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
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:

The percentage of responders in each treatment group was based on the histopathological regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36 and it was summarized for the mITT population. 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:

At 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:

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	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:

The percentage of responders in each treatment group was based on the histopathological regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36 and it was summarized for the PP Population. 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:

At 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:

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	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: Overview of Adverse Events (Safety Population)

End point title	Overview of Adverse Events (Safety Population)

End point description:

Treatment-Emergent Adverse Events (TEAE) was defined as AE with onset date on or after clinical trial treatment. One subject excluded due to receiving mixed treatment.

End point type	Secondary

End point timeframe:

With onset date on or after clinical trial treatment

End point values	VGX-3100 + EP	Placebo + EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	62		
Units: subjects				
Any AE	131	61		
Any pretreatment AE	18	7		
Any TEAE	131	61		
Any serious TEAE	13	6		
Any IP- or EP-related TEAE	114	56		
Any IP- or EP-related serious TEAE	0	0		
Any TEAE with CTCAE ≥3	19	7		
Any IP- or EP-related TEAE with CTCAE ≥3	3	2		
Any TEAE of special interest	0	0		
Any TEAE with treatment permanently discontinued	1	0		
Any TEAE leading to death	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Onset date on or after clinical trial treatment	
Adverse event reporting additional description:	
Treatment-Emergent Adverse Events (TEAE) was defined as AE with onset date on or after clinical trial treatment. One subject excluded due to receiving mixed treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	VGX-3100 + EP
Reporting group description:	
Eligible subjects received three 6-mg doses of VGX-3100 refrigerated formulation followed immediately by electroporation (EP) with the CELLECTRA™ 5PSP device. The first clinical trial treatment was administered on Day 0, the second at Week 4, and the third (final) at Week 12. The first clinical trial treatment was given as soon as possible following confirmation of the cervical HSIL diagnosis and HPV-16 and/or HPV-18 status but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC during screening, contemporaneous with the positive testing for HPV-16 and/or HPV-18.	
Reporting group title	Placebo + EP
Reporting group description:	
Eligible subjects received three placebo, followed immediately by electroporation (EP) with the CELLECTRA™ 5PSP device. The first clinical trial treatment was administered on Day 0, the second at Week 4, and the third (final) at Week 12. The first clinical trial treatment was given as soon as possible following confirmation of the cervical HSIL diagnosis and HPV-16 and/or HPV-18 status but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC during screening, contemporaneous with the positive testing for HPV-16 and/or HPV-18.	

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