

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

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

Results information

Result version number	v2 (current)
This version publication date	22 August 2018
First version publication date	26 July 2017
Version creation reason	<ul style="list-style-type: none">• Correction of full data set• Correction of start date needed.

Trial information**Trial identification**

Sponsor protocol code	HPV-003
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Inovio Pharmaceuticals, Inc
Sponsor organisation address	660 W Germantown Pike, Suite 110, Plymouth Meeting, PA, United States, 19462
Public contact	Inovio Pharmaceuticals, Inc, Inovio Pharmaceuticals, Inc, +1 267-440-4200, clinical.trials@inovio.com
Scientific contact	Inovio Pharmaceuticals, Inc, Inovio Pharmaceuticals, Inc, +1 267-440-4200, clinical.trials@inovio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	167
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

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

Arm title	Placebo + EP
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Arm description:

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

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

Reporting group title	VGX-3100 + EP
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Reporting group description:

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

Reporting group title	Placebo + EP
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Reporting group description:

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

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

End points

End points reporting groups

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

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

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

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

Statistical analyses

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

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

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

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

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

End point type	Primary
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End point timeframe:

Week 36

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

Statistical analyses

Statistical analysis title	VGX-3100 + EP versus Placebo + EP
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Statistical analysis description:

The primary hypothesis was that VGX-3100 + EP is superior to placebo + EP for the entire population.

Comparison groups	Placebo + EP v VGX-3100 + EP
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Number of subjects included in analysis	154
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.034
Method	Mehrotra's test
Parameter estimate	Percentage point difference
Point estimate	17.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	34.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	VGX-3100 + EP
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Reporting group description:

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

Reporting group title	Placebo + EP
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Reporting group description:

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported